FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY'S DOCKET NUMBER: SCH 1806

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 09/831506

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/08478	9 NOVEMBER 1999	10 NOVEMBER 1998

TITLE OF INVENTION

ANTHRANILIC ACID AMIDES AND THE USE THEREOF AS MEDICAMENTS

APPLICANT(S) FOR DO/EO/US

HUTH, Andreas, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR §1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/831506	PCT/EP99/08478	SCH 1806

17. ☒ The following fees are submitted:		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):			
Search Report has been prepared by the EPO or JPO	$860.00		
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$690.00		
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$710.00		
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1000.00		
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).			

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	15 - 20 =	0	x $ 18.00	$0.00	
Independent claims	3 - 3 =	0	x $ 80.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00		
TOTAL OF ABOVE CALCULATIONS =				$860.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).					
SUBTOTAL =				$860.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$860.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$860.00	
				Amount to be refunded:	
				charged:	

a. ■ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

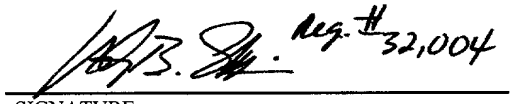
SEND ALL CORRESPONDENCE TO: Customer Number 23,599

23599

PATENT TRADEMARK OFFICE

Filed: 10 MAY 2001

AJZ:kms



SIGNATURE

Reg. # 32,004

Anthony J. Zelano

NAME

27,969

REGISTRATION NUMBER

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/EP99/08578
International Filing Date	:	9 NOVEMBER 1999
Priority Date(s) Claimed	:	10 NOVEMBER 1998
Applicant(s) (DO/EO/US)	:	HUTH, Andreas, et al.

Title: ANTHRANILIC ACID AMIDES AND THEIR USE AS PHARMACEUTICAL AGENTS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

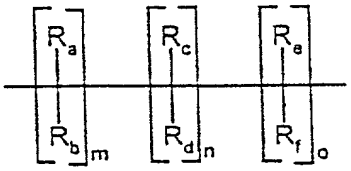
IN THE CLAIMS:

3. (Amended) Compounds of general formula I according to claim 1, in which

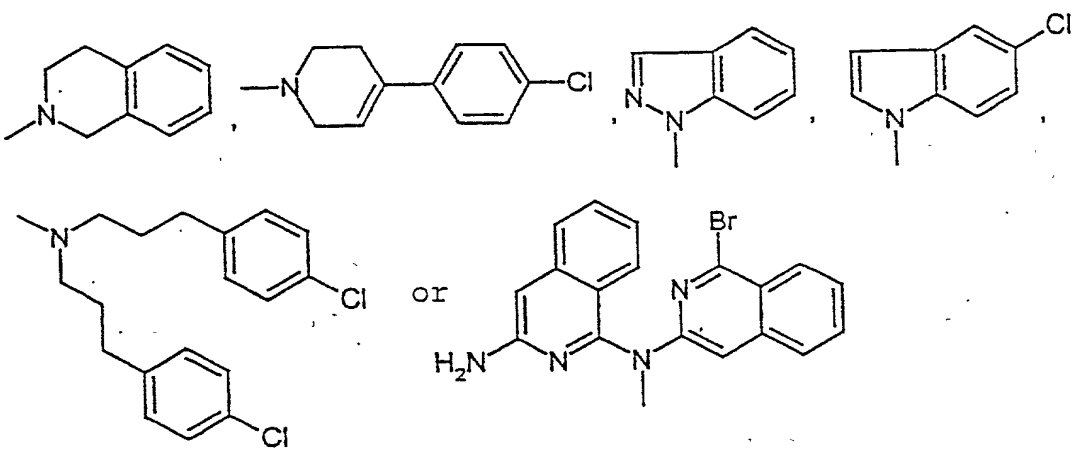
A stands for the group $=NR^2$,

W stands for oxygen, sulfur or two hydrogen atoms,

Z stands for the group $=NR^{10}$, =N, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

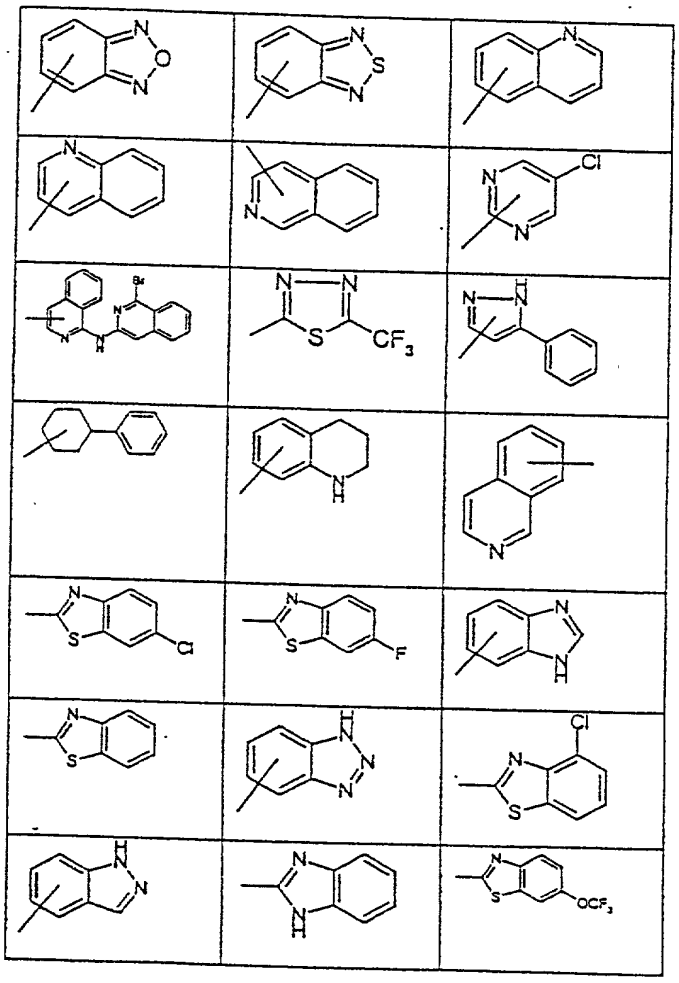
q stands for 1-6,

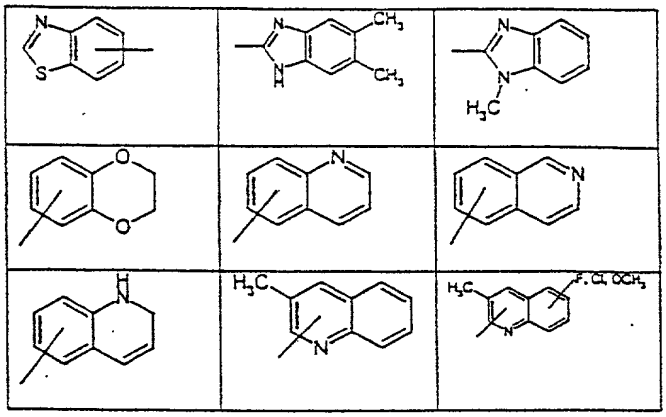
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, p-chlorophenyl, p-methylphenyl, p-methoxyphenyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl, or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, trifluoromethyl, or for the group

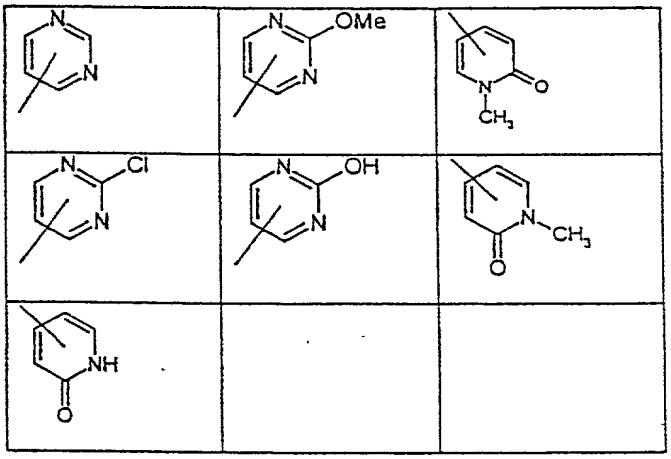




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl, or phenyl, or 1,2,3,4-tetrahydronaphthyl that is substituted by hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

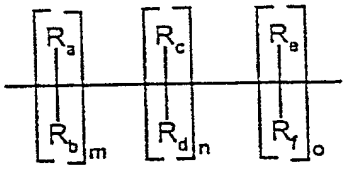
as well as their isomers and salts.

4. (Amended) Compounds of general formula I according to claim 1, in which

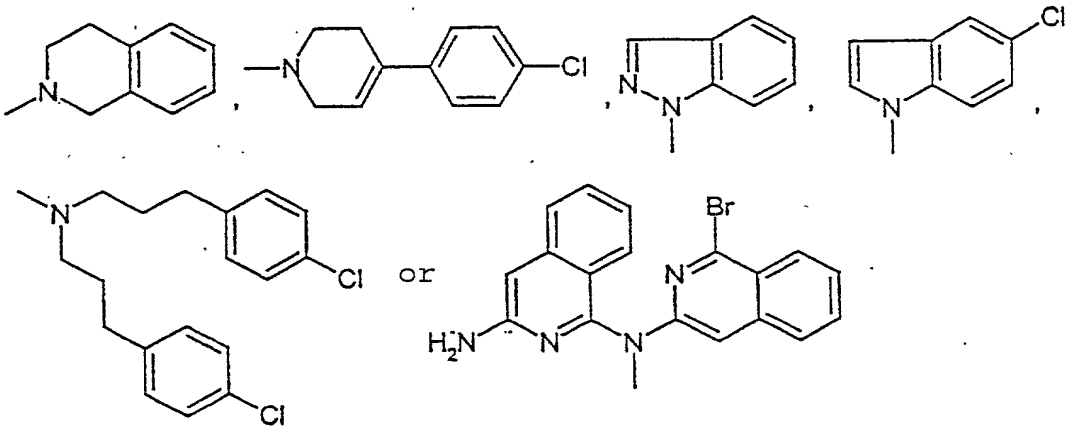
A stands for the group $=NR^2$,

W stands for oxygen,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

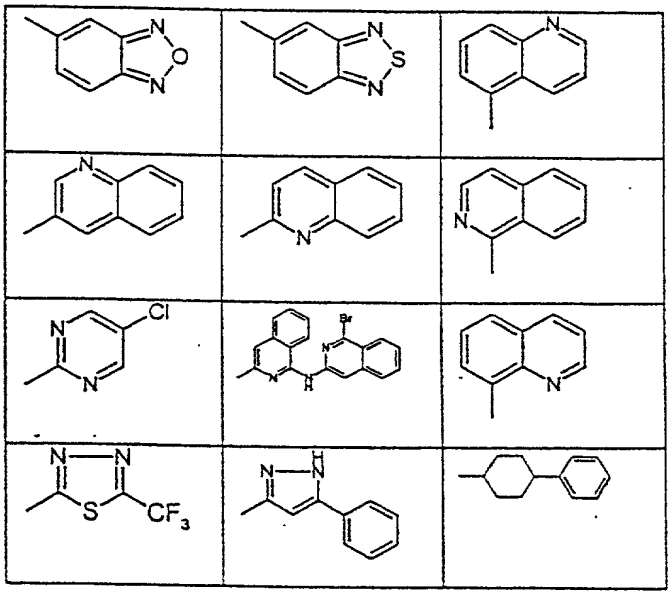
q stands for 1-6,

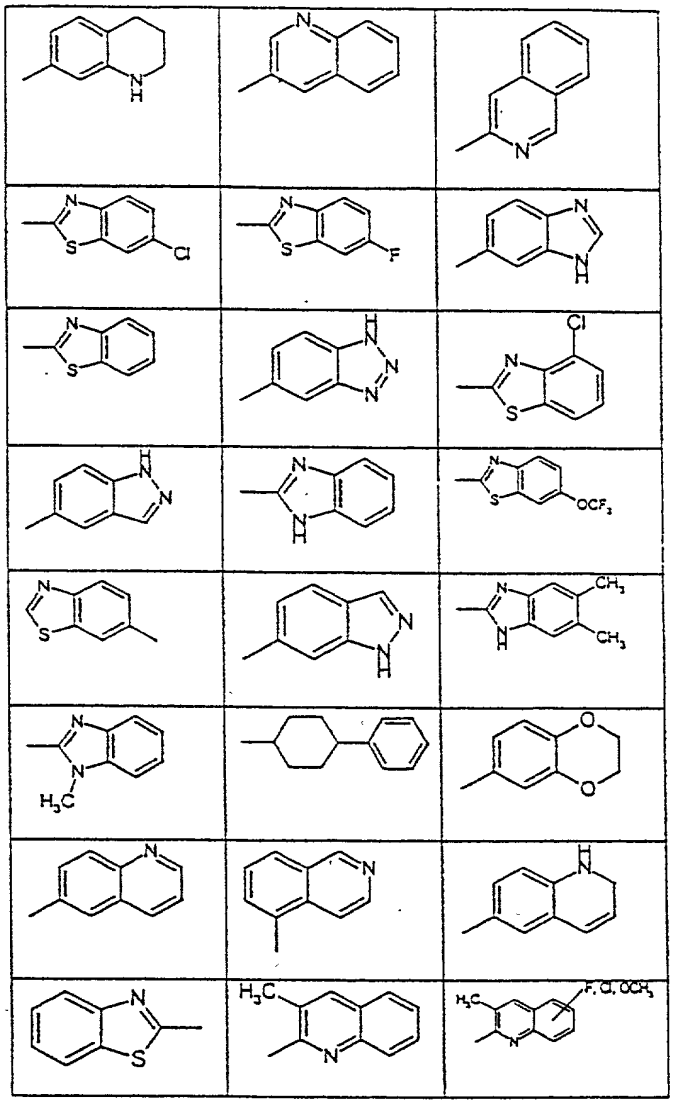
R_a, R_b, R_c, R_d, R_e, R_f independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

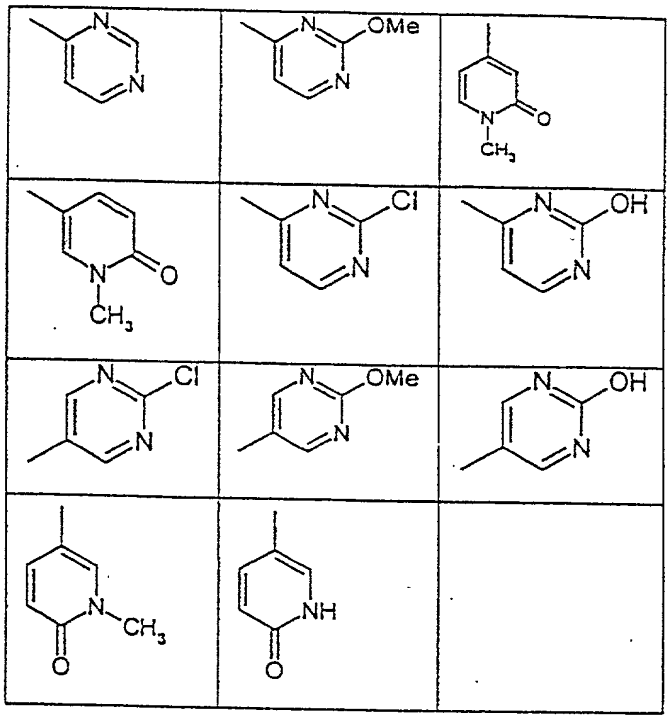




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3	stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6,	independently of one another, stand for hydrogen, halogen, methyl, methoxy, or trifluoromethyl,
R^4 and R^7,	independently of one another, stand for hydrogen and halogen,
R^9	stands for hydrogen,
R^{10}	stands for hydrogen or methyl,

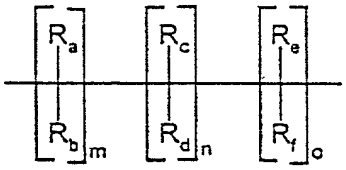
as well as their isomers and salts.

5. (Amended) Compounds of general formula I according to claim 1, in which

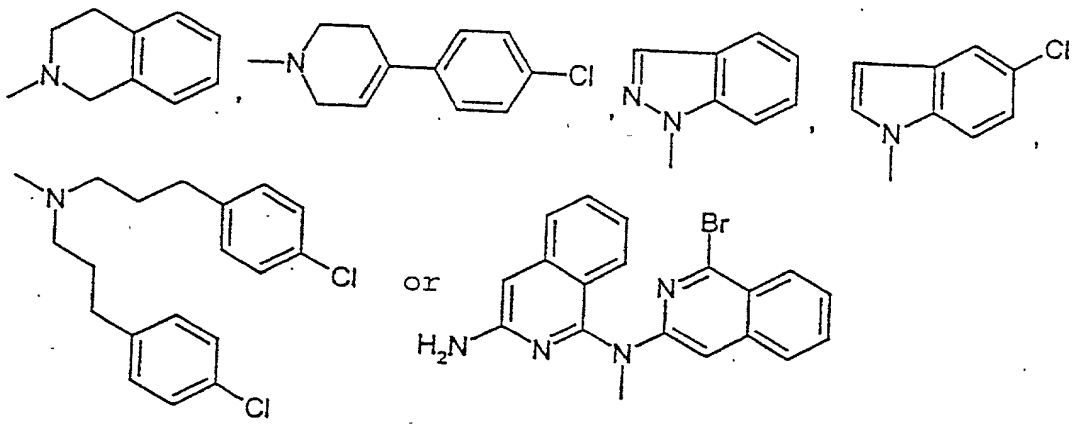
A stands for the group $=NR^2$,

W stands for sulfur,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



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q stands for 1-6,

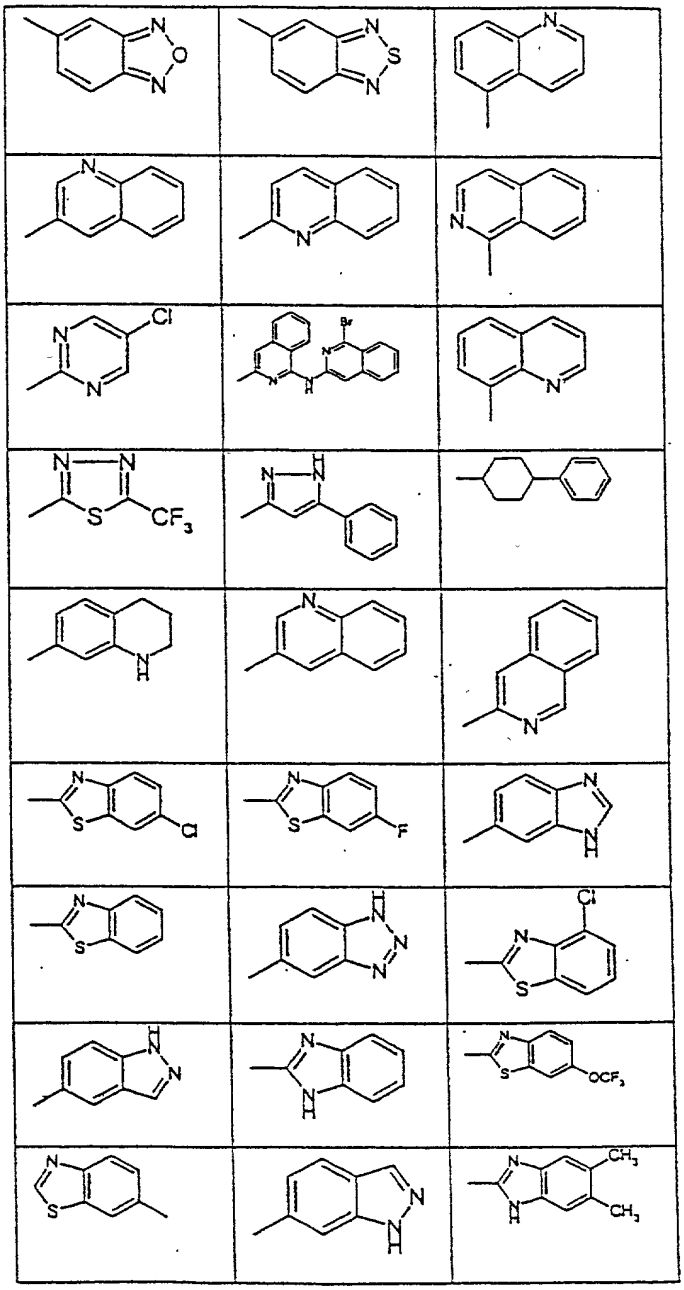
R_a, R_b, R_c, R_d, R_e, R_f independently of one another,

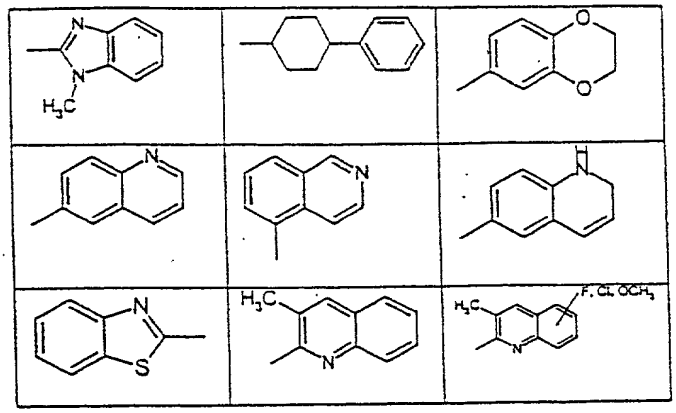
stand for hydrogen or methyl or thegroup $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

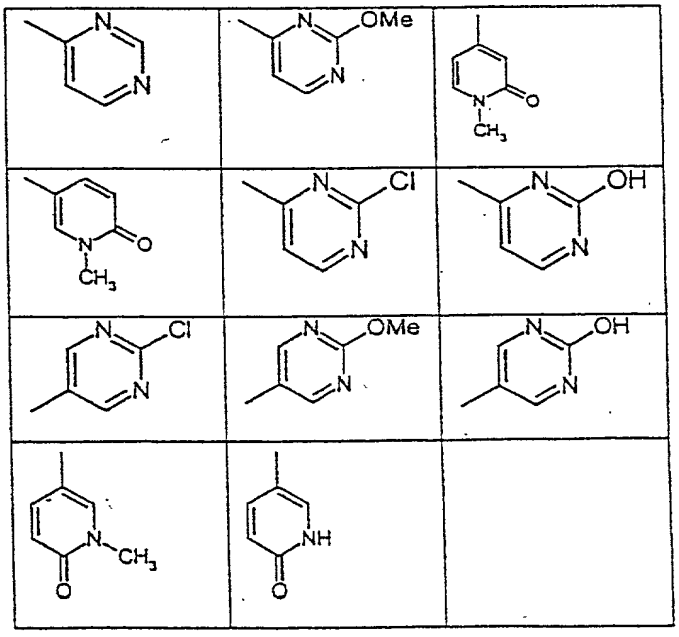




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

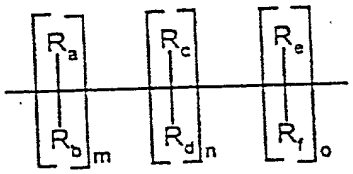
as well as their isomers and salts.

6. (Amended) Compounds of general formula I according to claim 1, in which

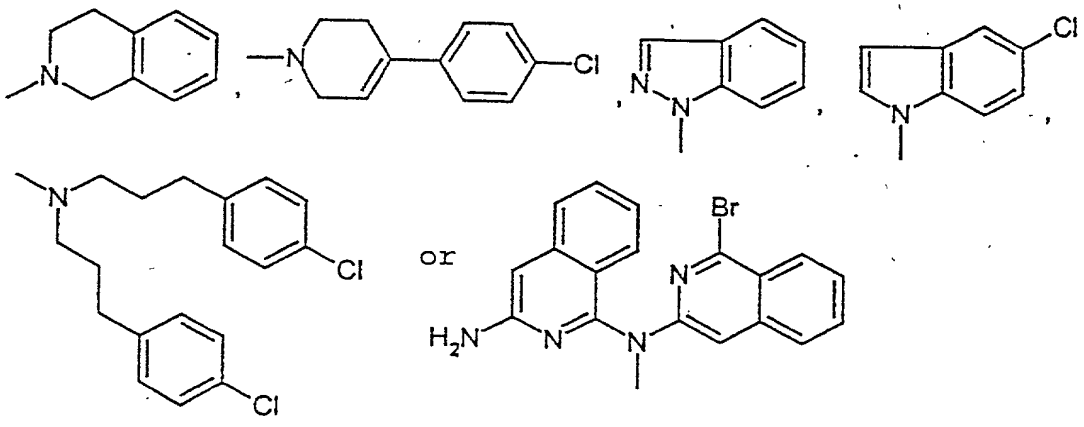
A stands for the group $=NR^2$,

W stands for two hydrogen atoms,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z, and R^1 together form the group



m, n and o stand for 0-3,

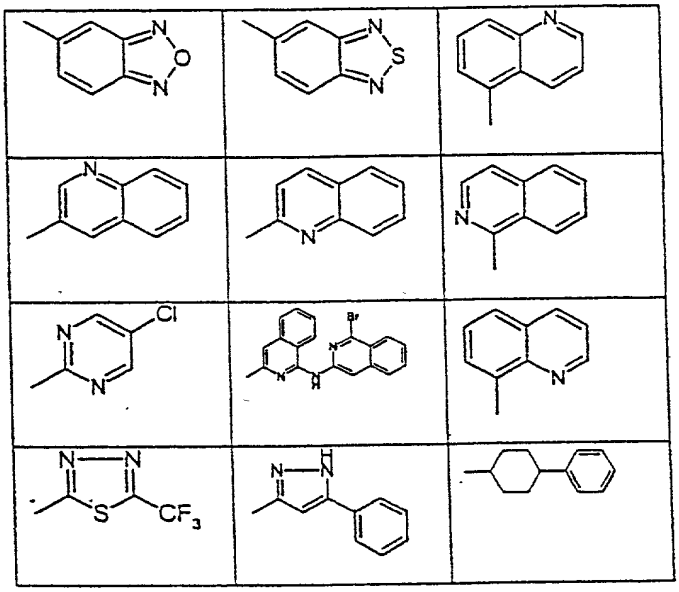
q stands for 1-6,

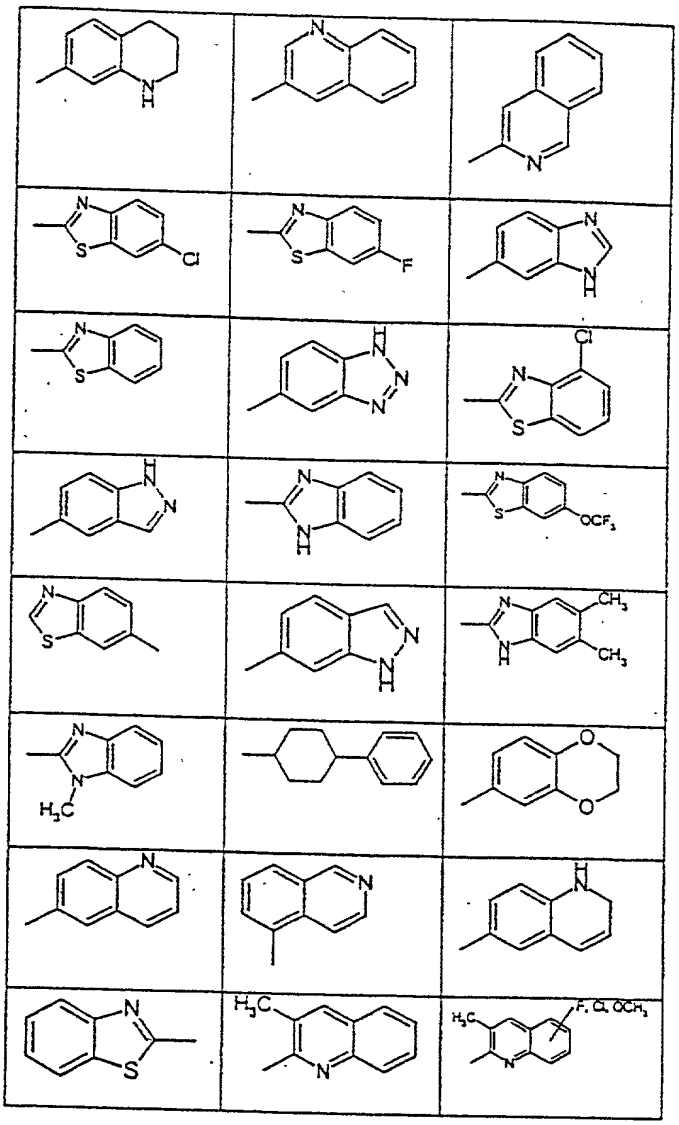
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

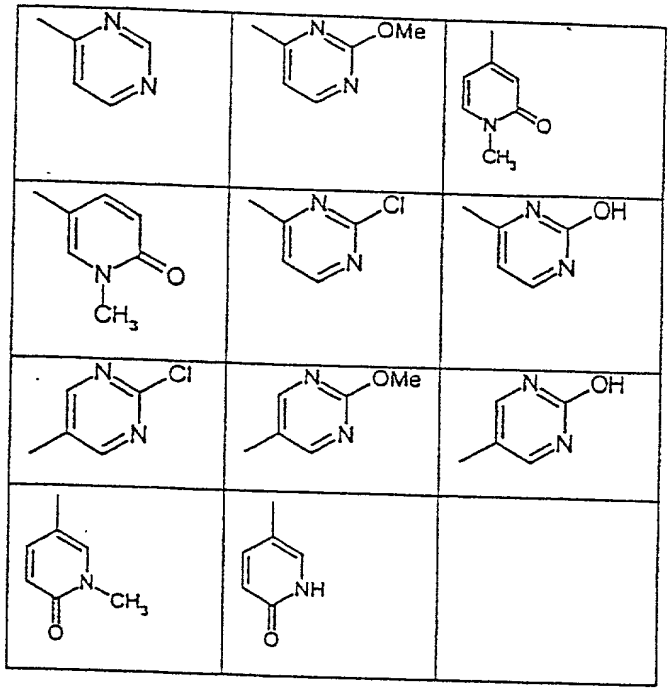




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3	stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^4 and R^7,	independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,
R^5 and R^6,	independently of one another, stand for hydrogen and halogen,
R^9	stands for hydrogen,
R^{10}	stands for hydrogen or methyl,

as well as their isomers and salts.

7. (Amended) Use of the compounds of general formula I, according to claim 1, for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

8. (Amended) Pharmaceutical agent that contains at least one compound according to claim 1.

10. (Amended) Compounds according to claim 6 and pharmaceutical agents according to claim 6 with suitable formulations and vehicles.

11. (Amended) Use of the compounds of formula I according to claim 1 as inhibitors of tyrosine kinases KDR and FLT.

12. (Amended) Use of the compounds of general formula I according to claim 1 in the form of a pharmaceutical preparation for enteral, parenteral and oral administration.

15. (Amended) Compounds of general formula V according to claim 13 for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Respectfully submitted,

Reg. # 32,004

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicants
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AJZ:jmm

Filed: 10 MAY 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

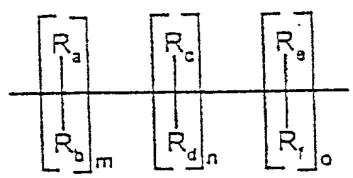
Claims 3-8, 10-12 and 15 have been amended as follows:

3. (Amended) Compounds of general formula I according to ~~claims~~ claim 1 ~~and 2~~, in which

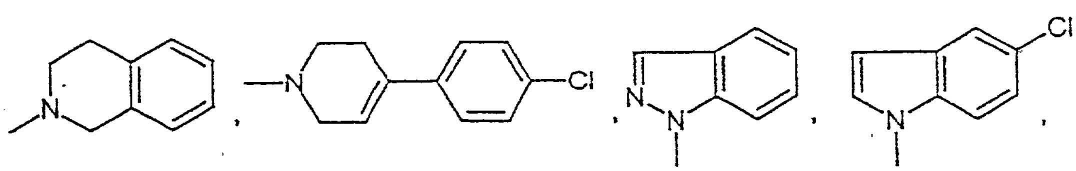
A stands for the group $=NR^2$,

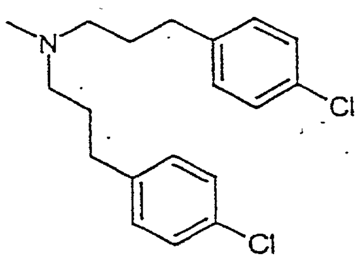
W stands for oxygen, sulfur or two hydrogen atoms,

Z stands for the group $=NR^{10}$, $=N$, $-N(R^{10})-(CH_2)_q-$ or the group

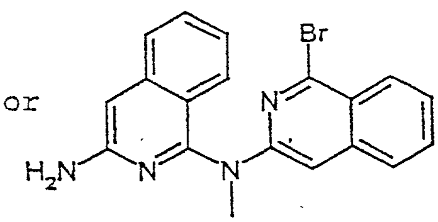


or A, Z and R^1 together form the group





or



m, n and o stand for 0-3,

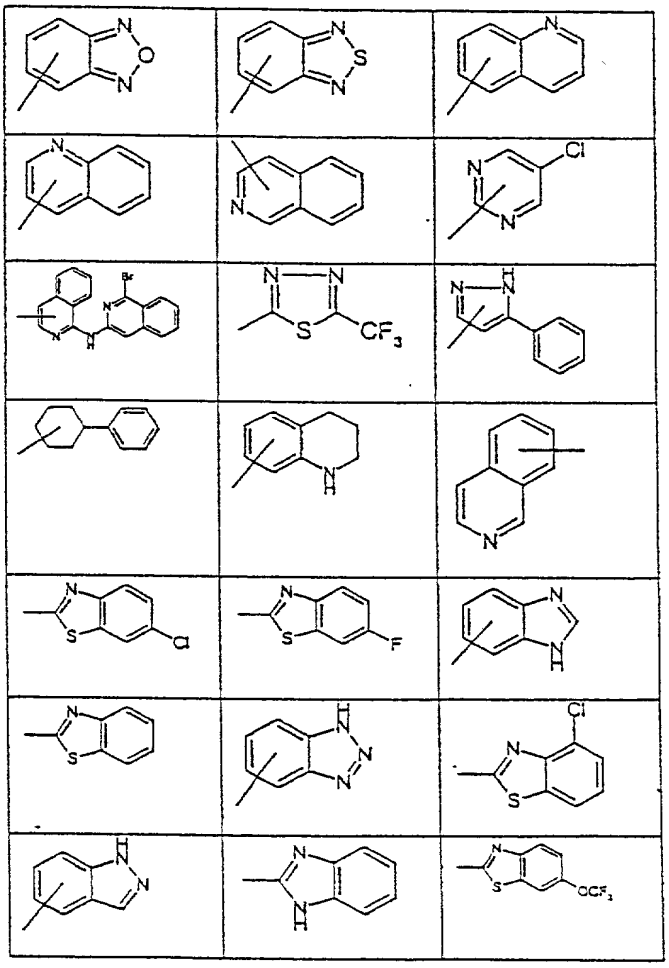
q stands for 1-6,

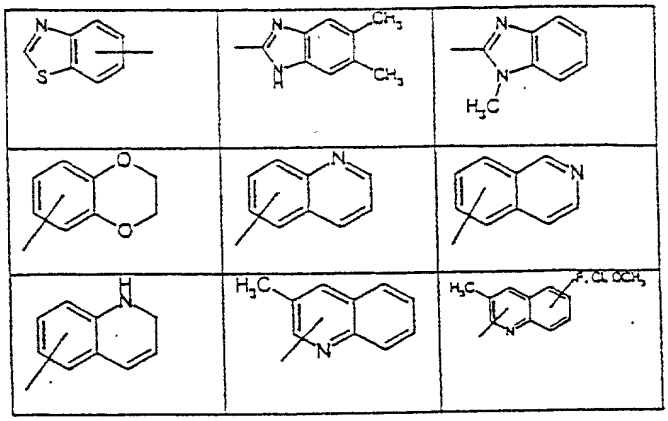
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, p-chlorophenyl, p-methylphenyl, p-methoxyphenyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl, or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, trifluoromethyl, or for the group

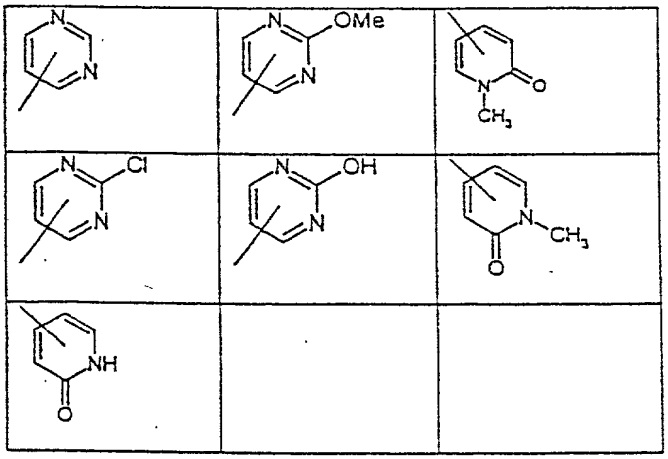




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl, or phenyl, or 1,2,3,4-tetrahydronaphthyl that is substituted by hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

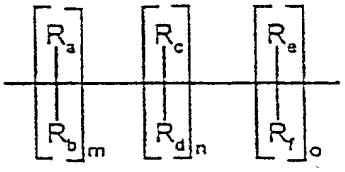
as well as their isomers and salts.

4. (Amended) Compounds of general formula I according to ~~claims~~ claim 1 ~~to 3~~, in which

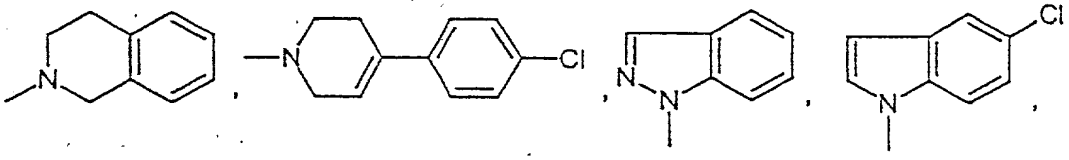
A stands for the group $=NR^2$,

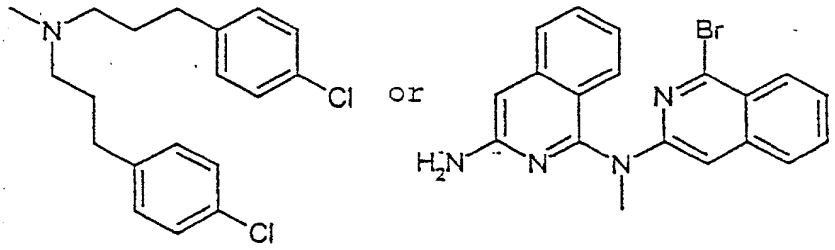
W stands for oxygen,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-$ $(CH_2)_q$- or the group



or A, Z and R^1 together form the group





m, n and o stand for 0-3,

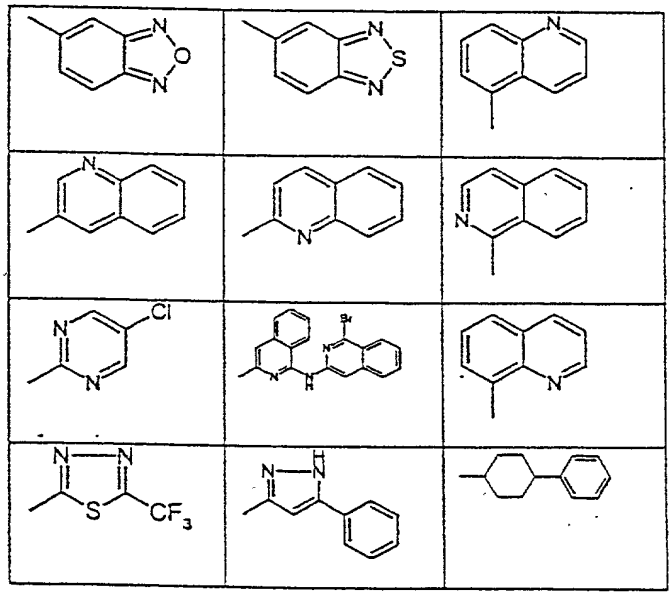
q stands for 1-6,

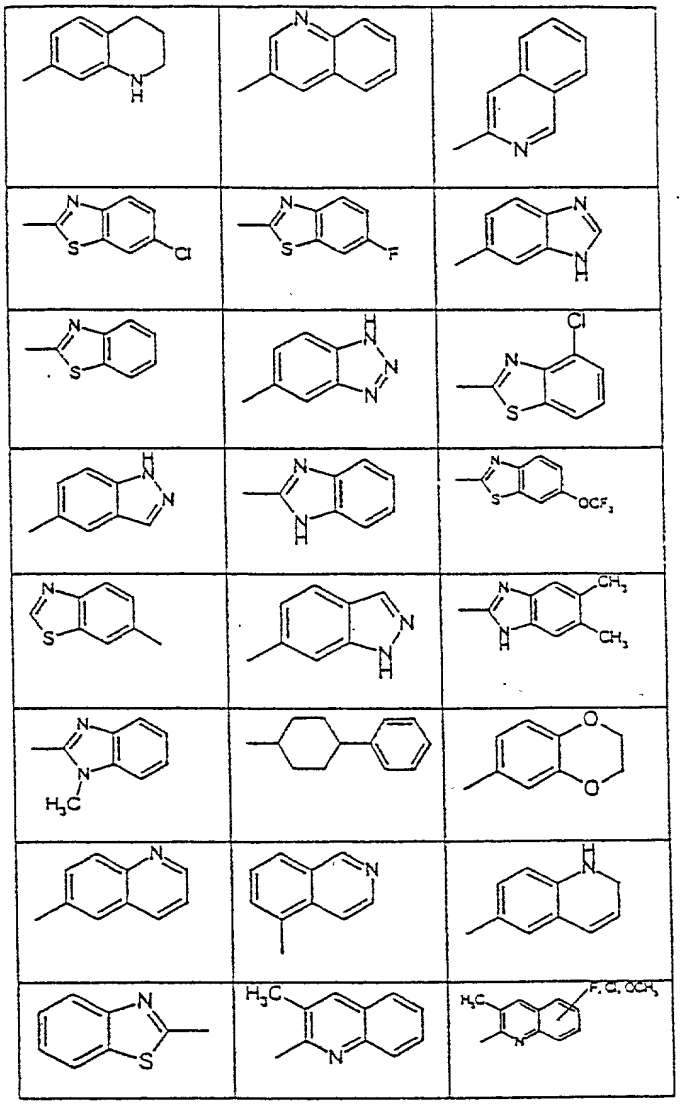
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

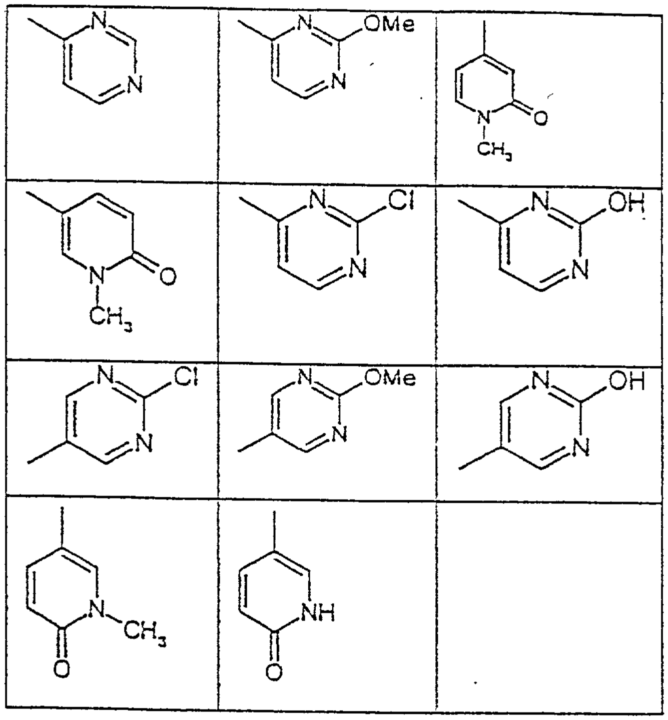




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6,	independently of one another, stand for hydrogen, halogen, methyl, methoxy, or trifluoromethyl,
R^4 and R^7,	independently of one another, stand for hydrogen and halogen,
R^9	stands for hydrogen,
R^{10}	stands for hydrogen or methyl,

as well as their isomers and salts.

R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy, or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

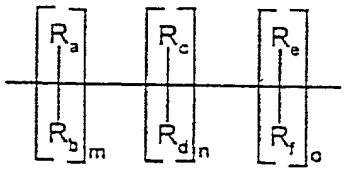
as well as their isomers and salts.

5. (Amended) Compounds of general formula I according to ~~claims~~ claim 1 ~~to 3~~, in which

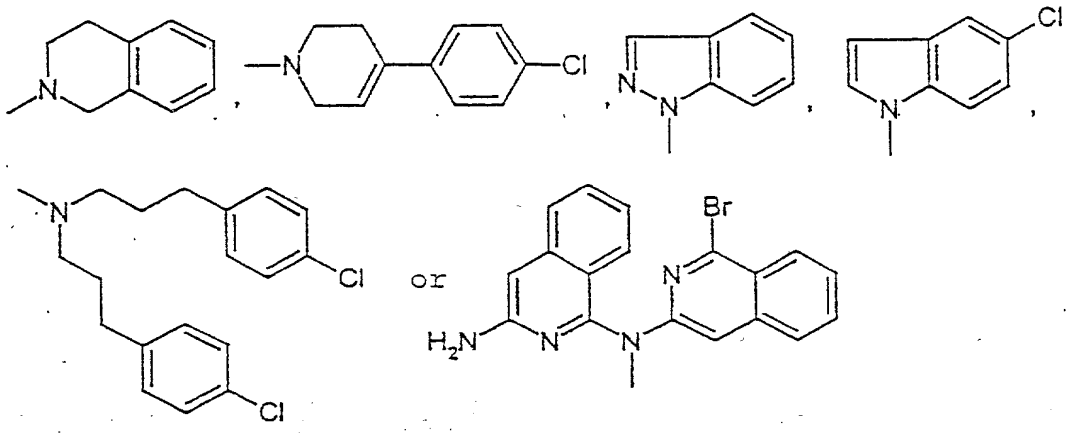
A stands for the group $=NR^2$,

W stands for sulfur,

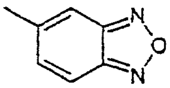
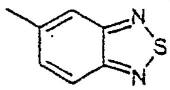
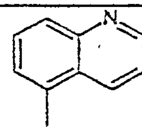
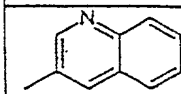
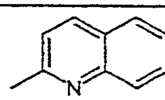
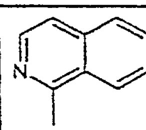
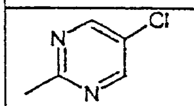
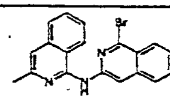
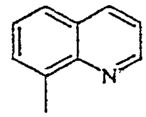
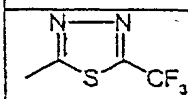
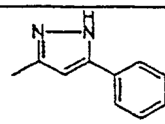
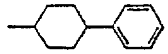
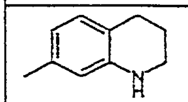
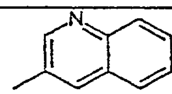
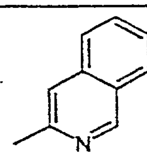
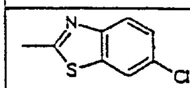
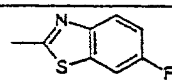
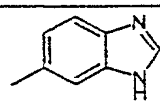
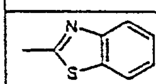
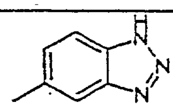
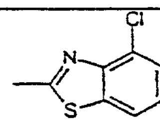
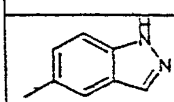
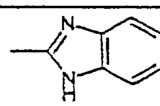
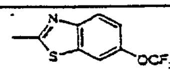
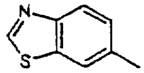
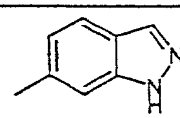
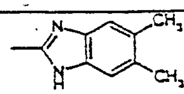
Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group

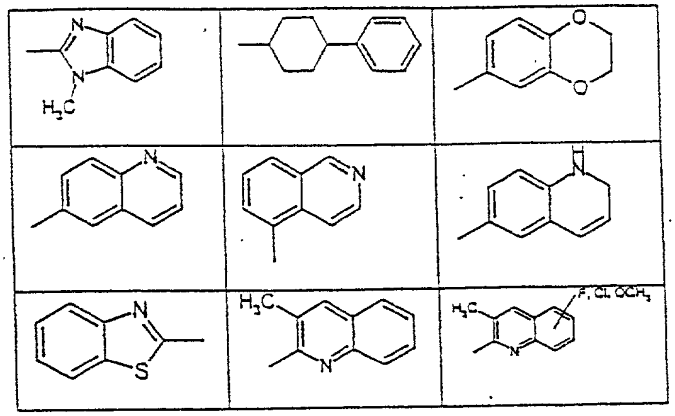


or A, Z and R^1 together form the group



m, n and o	stand for 0-3,
q	stands for 1-6,
R_a, R_b, R_c, R_d, R_e, R_f,	independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,
X	stands for the group $=NR^9$ or $=N-$,
Y	stands for the group $-CH_2-$,
R^1	stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

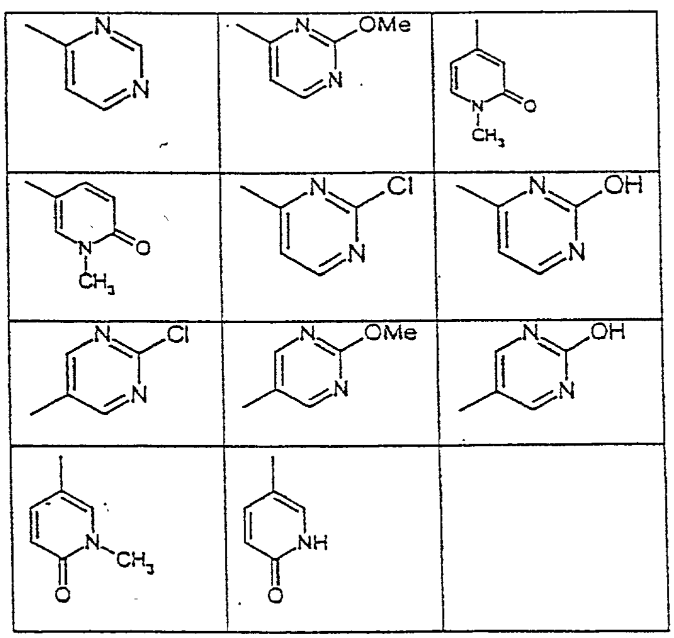
		
		
		
		
		
		
		
		
		



whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

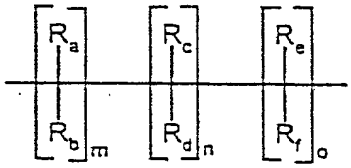
as well as their isomers and salts.

6. (Amended) Compounds of general formula I according to ~~claims~~ claim 1 ~~to 3~~, in which

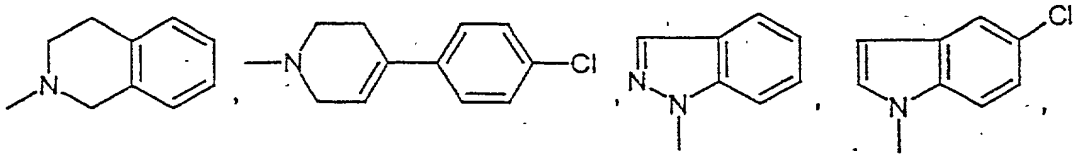
A stands for the group $=NR^2$,

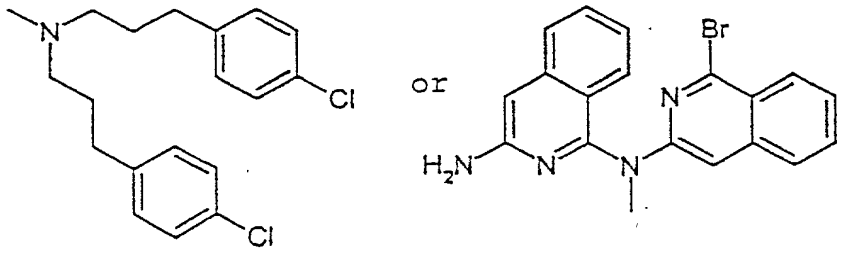
W stands for two hydrogen atoms,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z, and R^1 together form the group





m, n and o stand for 0-3,

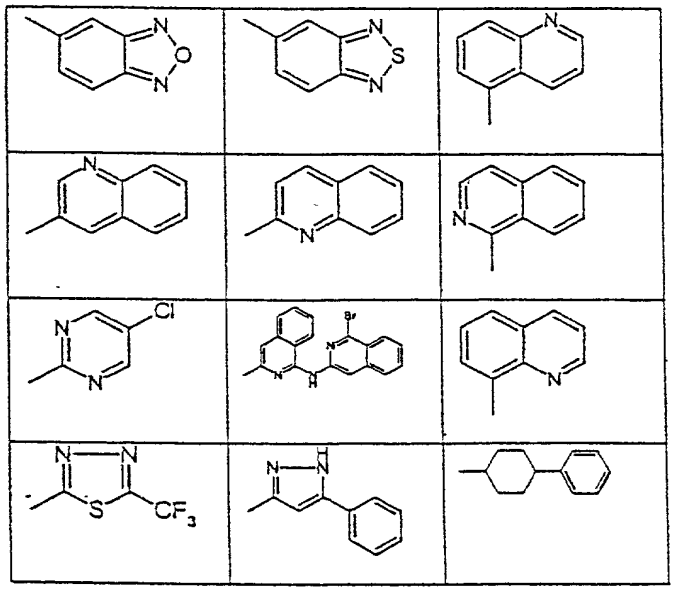
q stands for 1-6,

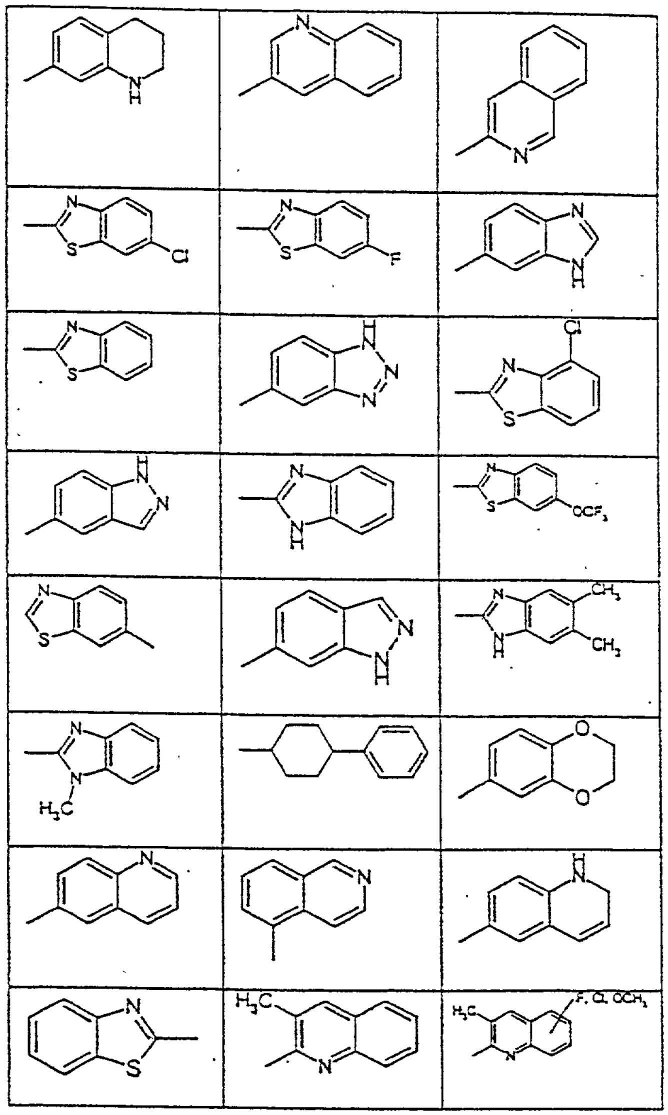
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

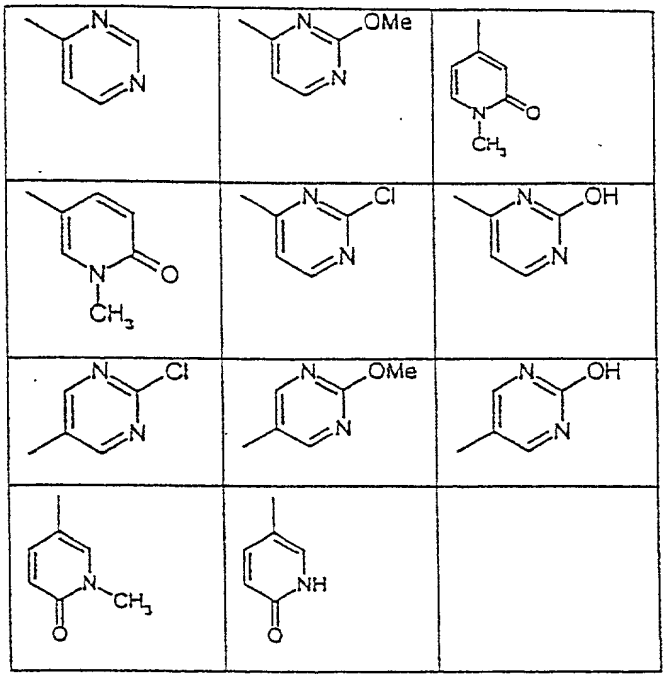




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^4 and R^7, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^5 and R^6, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

as well as their isomers and salts.

7. (Amended) Use of the compounds of general formula I, according to ~~claims~~ claim 1 ~~to 6~~, for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

8. (Amended) Pharmaceutical agent that contains at least one compound according to ~~claims~~ claim 1 ~~to 6~~.

10. (Amended) Compounds according to ~~claims 1 to~~ claim 6 and pharmaceutical agents according to ~~claims~~ claim 6 ~~and 8~~ with suitable formulations and vehicles.

11. (Amended) Use of the compounds of formula I according to ~~claims~~ claim 1 ~~to 6~~ as inhibitors of tyrosine kinases KDR and FLT.

12. (Amended) Use of the compounds of general formula I according to ~~claims~~ claim 1 ~~to 6~~ in the form of a pharmaceutical preparation for enteral, parenteral and oral administration.

15. (Amended) Compounds of general formula V according to ~~claims~~ claim 13 ~~and 14~~ for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome,

transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

Anthranilic Acid Amides and their Use as Pharmaceutical Agents

The invention relates to anthranilic acid amides and their use as pharmaceutical agents for treatment of diseases that are triggered by persistent angiogenesis as well as their intermediate products for the production of anthranilic acid amides.

Persistent angiogenesis can be the cause of various diseases such as psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, and arteriosclerosis or can result in a progression of these diseases.

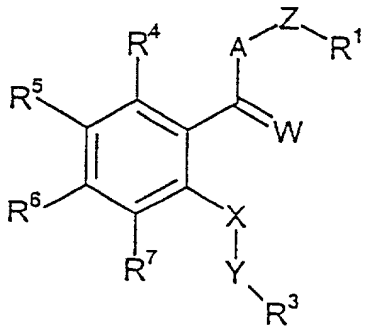
A direct or indirect inhibition of the VEGF receptor can be used for the treatment of such diseases and other VEGF-induced pathological angiogenesis and vascular permeable conditions, such as tumor vascularization. For example, it is known that by soluble receptors and antibodies against VEGF, the growth of tumors can be inhibited.

Persistent angiogenesis is induced by the VEGF factor via its receptor. So that VEFG can exert this action, it is

necessary that VEGF bonds to the receptor and a tyrosine phosphorylation is brought about.

Phenyl-anthranilamide derivatives are already known that are used as angiotensin II-antagonists (EP 564 356) and as antiinflammatory agents and anti-ulcera compounds (U.S. 3,409,668).

It has now been found that compounds of general formula I



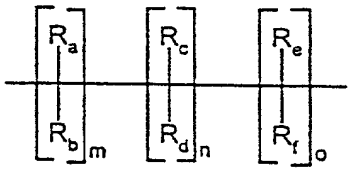
I

in which

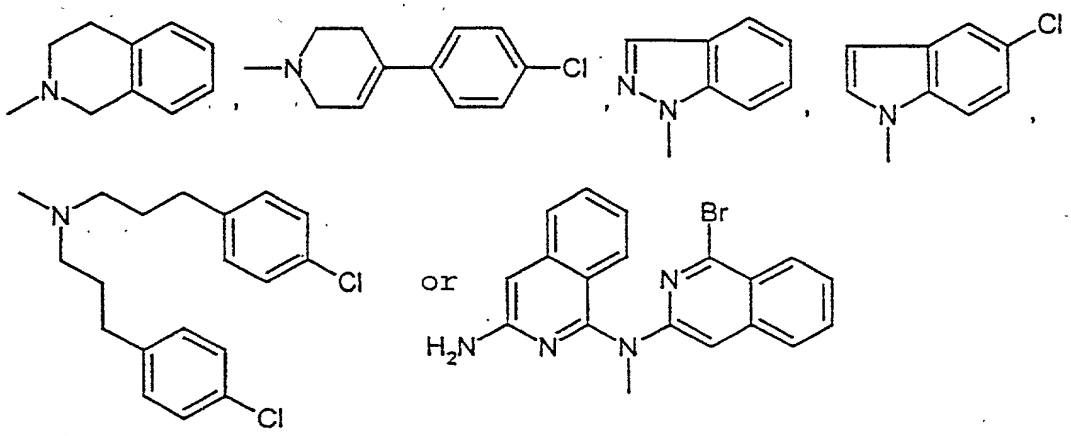
A stands for the group $=NR^2$,

W stands for oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,

Z stands for the group $=NR^{10}$ or =N-, $-N(R^{10})-(CH_2)_q-$, branched or unbranched C_{1-6} alkyl or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

q stands for 1-6,

R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen, C_{1-4} alkyl or the group $=NR^{10}$, and/or R_a and/or R_b can form a bond with R_c and/or R_d or R_c can form a bond with R_e and/or R_f, or up to two of radicals R_a-R_f can close a bridge with up to 3 C-atoms each to form R^1 or R^2,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-(CH_2)_p$,

p stands for 1-4,

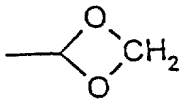
R^1 stands for C_{1-6} alkyl that is unsubstituted or is optionally substituted in one or more places with

halogen, C_{1-6} alkyl, in one or more places with halogen, or aryl or heteroaryl that is substituted with C_{1-6} alkoxy, with the exception of compounds in which aryl is bonded right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or C_{1-6} alkyl or forms a bridge with up to 3 ring members with R_a-R_f from Z or to form R_1,

R^3 stands for monocyclic or bicyclic aryl or heteroaryl that is unsubstituted or optionally substituted in one or more places with halogen, C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy,

R^4, R^5, R^6, and R^7, independently of one another, stand for hydrogen, halogen, or C_{1-6} alkoxy, C_{1-6} alkyl or C_{1-6} carboxylalkyl that is unsubstituted or optionally substituted in one or more places with halogen, or R^5 and R^6 together form the group

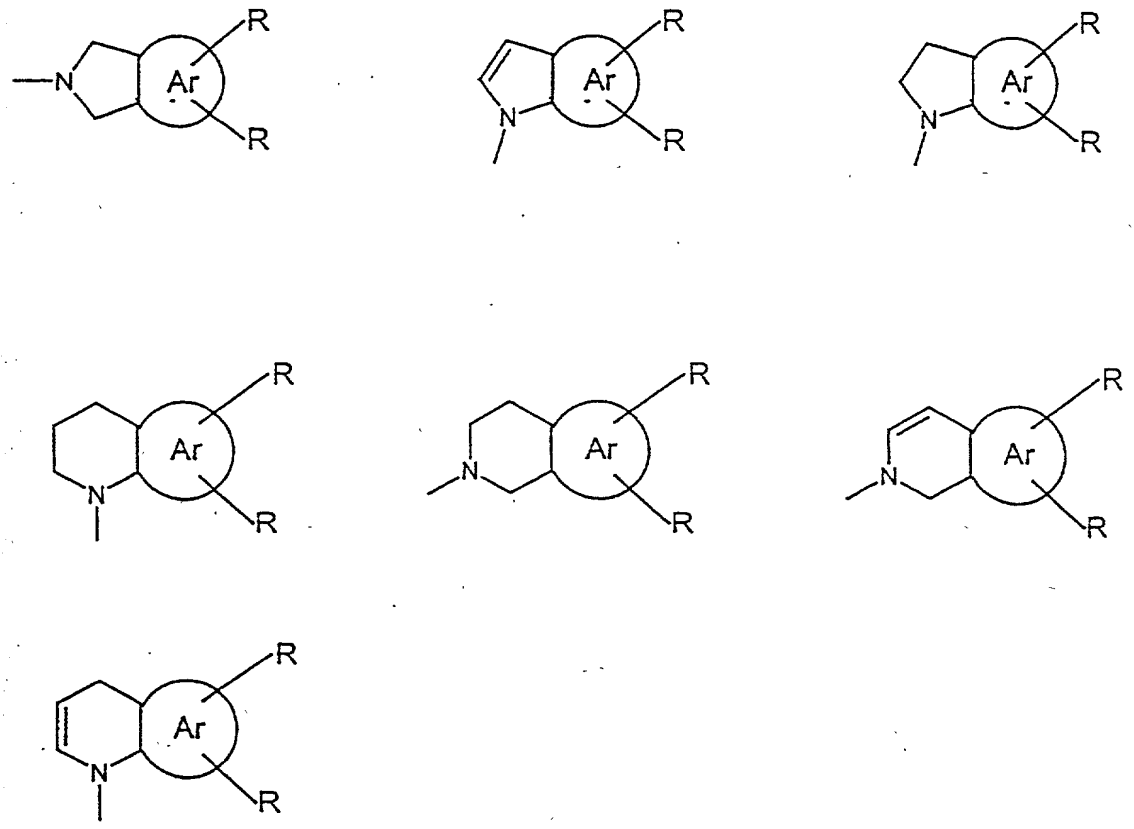


R^8, R^9, and R^{10}, independently of one another, stand for hydrogen or C_{1-6} alkyl,

as well as their isomers and salts, stop a tyrosine phosphorylation or persistent

angiogenesis and thus prevent the growth and propagation of tumors.

If R^2 forms a bridge to R^1, heterocycles are produced to which R^1 is fused. For example, there can be mentioned:



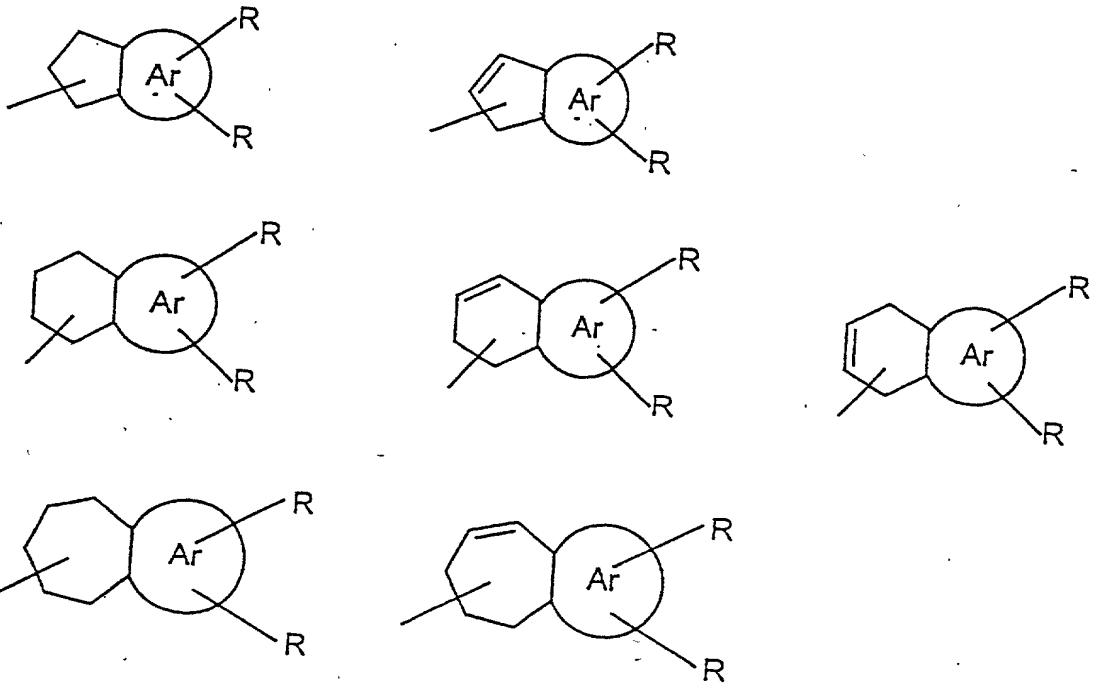
If R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, represent hydrogen or C_{1-4} alkyl, Z forms an alkyl chain.

If R_a and/or R_b form a bond with R_c and/or R_d or R_c and/or R_d form a bond with R_e and/or R_f, Z stands for an alkenyl or alkinyl chain.

If R_a-R_f form a bridge on their own, Z represents a cycloalkyl or cycloalkenyl group.

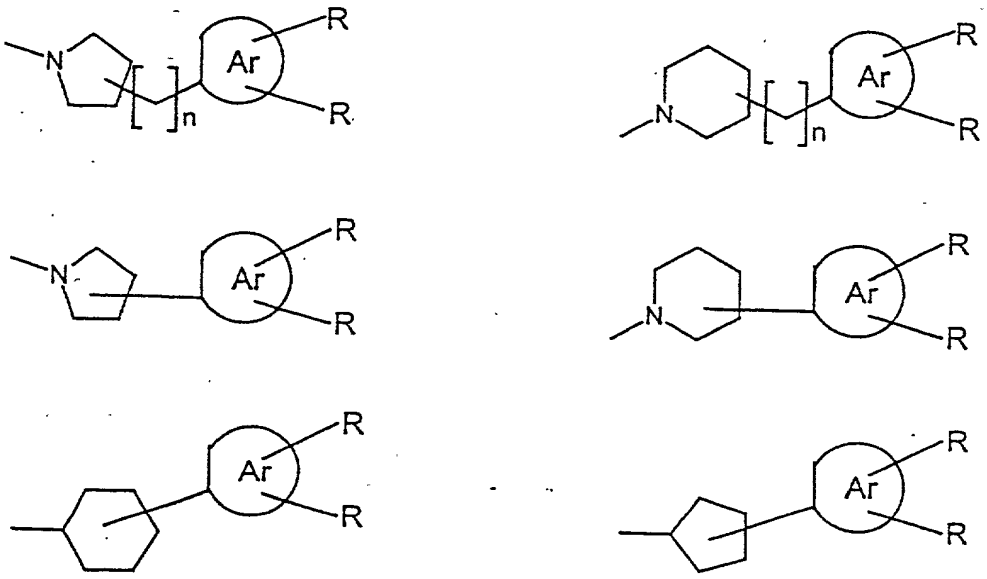
If up to two of radicals R_a-R_f form a bridge with up to 3 C atoms to R^1, Z together with R^1 is a benzo- or hetaryl-condensed (Ar) cycloalkyl.

For example, there can be mentioned:



If one of radicals R_a-R_f closes a bridge to form R^2, a nitrogen heterocycle that can be separated from R^1 by a group is formed.

For example, there can be mentioned:



Alkyl is defined in each case as a straight-chain or branched alkyl radical, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl or hexyl, whereby C_{1-4} alkyl radicals are preferred.

Cycloalkyl is defined respectively as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Cycloalkenyl is defined respectively as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, whereby the linkage can take place both to the double bond and to the single bonds.

Halogen is defined respectively as fluorine, chlorine, bromine or iodine.

The alkenyl and alkinyl substituents are in each case straight-chain or branched and contain 2-6 C atoms, preferably 2-4 C atoms. For example, the following radicals can be mentioned: vinyl, propen-1-yl, propen-2-yl, but-1-en-1-yl, but-1-en-2-yl, but-2-en-1-yl, but-2-en-2-yl, 2-methyl-prop-2-en-1-yl, 2-methyl-prop-1-en-1-yl, but-1-en-3-yl, ethinyl, prop-1-in-1-yl, but-1-in-1-yl, but-2-in-1-yl, but-3-en-1-yl, allyl.

In each case, the aryl radical has 6-12 carbon atoms, such as, for example, naphthyl, biphenyl and especially phenyl.

In each case, the heteroaryl radical can be benzocondensed. For example, there can be mentioned as 5-ring heteroaromatic compounds: thiophene, furan, oxazole, thiazole, imidazole, pyrazole and benzo derivatives thereof, and as 6-ring-heteroaromatic compounds pyridine, pyrimidine, triazine, quinoline, isoquinoline and benzo derivatives, whereby in the case of benzocondensed heteroaryl radicals, the binding can be both to the heterocycle and to the benzo ring.

In each case, the aryl radical and the heteroaryl radical can be substituted by the same or a different component in 1, 2 or 3 places with halogen, C_{1-4} alkoxy, nitro, trifluoromethyl, trifluoromethoxy, cyano, SO_qR^5 or C_{1-4} alkyl, whereby q stands for 0-2.

If an acid group is included, the physiologically compatible salts of organic and inorganic bases are suitable as salts, such as, for example, the readily soluble alkali and alkaline-earth salts as well as N-methyl-glucamine, dimethyl glucamine, ethyl glucamine, lysine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-amino-methane, aminopropanediol, Sovak base, 1-amino-2,3,4-butanetriol.

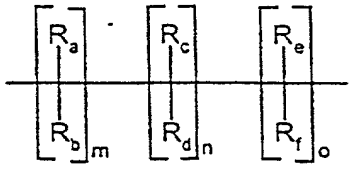
If a basic group is included, the physiologically compatible salts of organic and inorganic acids are suitable, such as hydrochloric acid, sulfuric acid, phosphoric acid, citric acid, tartaric acid, i.a.

Those compounds of general formula I in which

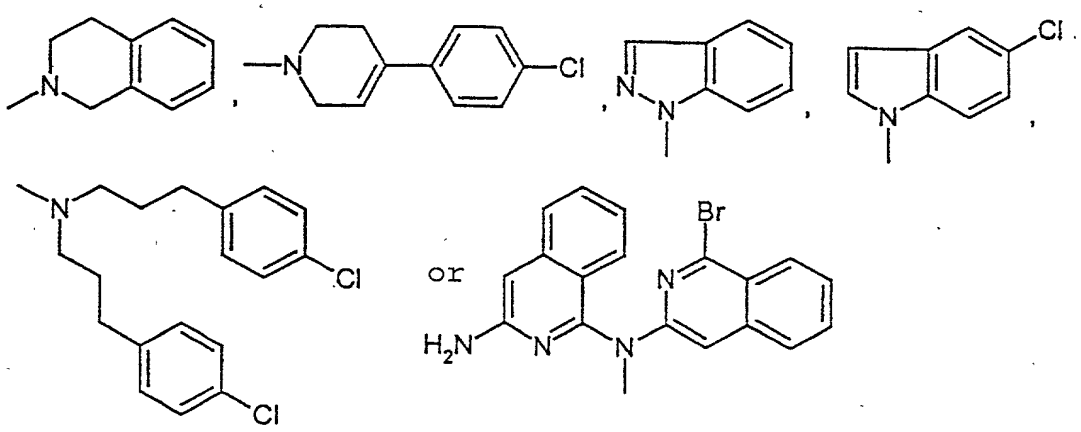
A stands for the group $=NR^2$,

W stands for oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,

Z stands for the group $=NR^{10}$, =N- or $-N(R^{10})-(CH_2)_q-$, branched or unbranched C_{1-6} alkyl or the group



or A, Z and R^1 together form the group



m, n, and o stand for 0-3,

q stands for 1-6,

R_a, R_b, R_c, R_d, R_e and R_f, independently of one another, stand for hydrogen, C_{1-4} alkyl or the group $=NR^{10}$,

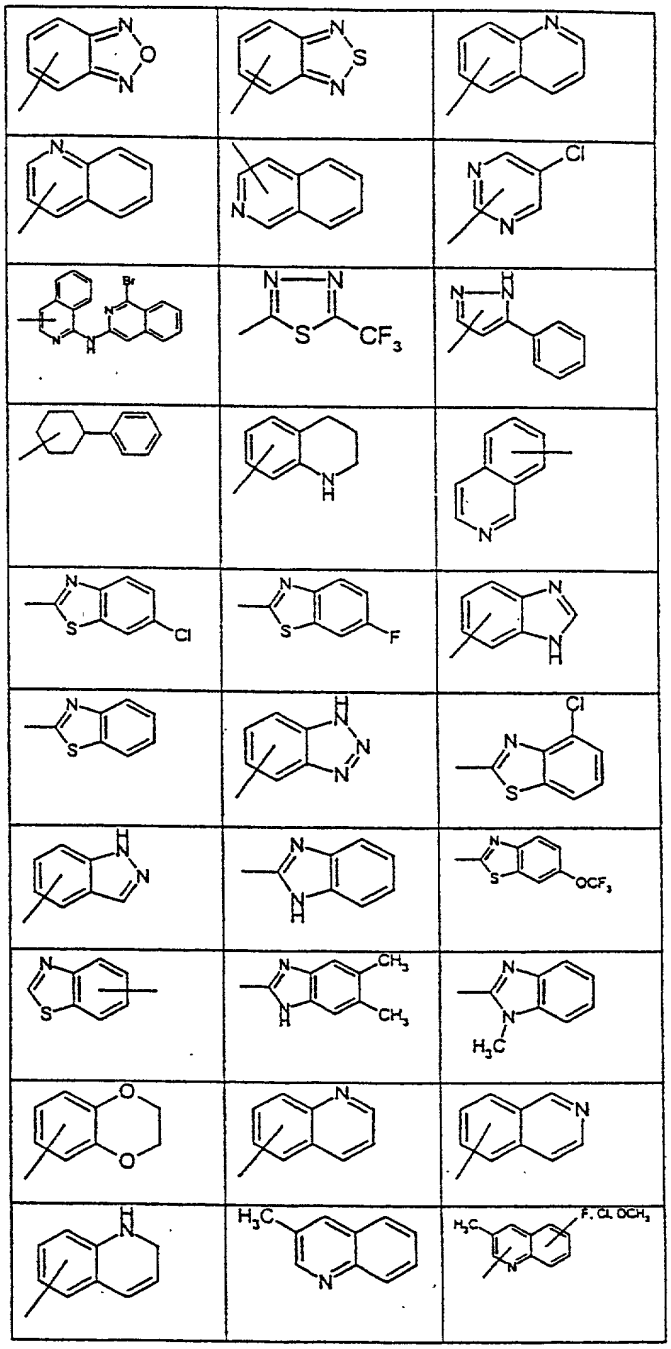
X stands for the group $=NR^9$ or =N-,

Y stands for the group $-(CH_2)_p$,

p stands for 1-4,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-

C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

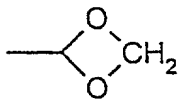


whereby phenyl, substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or C_{1-6} alkyl or forms a bridge with up to 3 ring members with R_a-R_f from Z or to form R_1,

R^3 stands for monocyclic or bicyclic aryl or monocyclic or bicyclic heteroaryl that is unsubstituted or optionally substituted in one or more places with halogen, C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy,

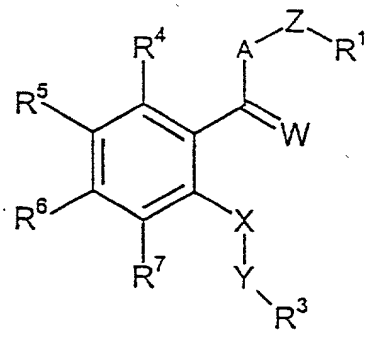
R^4, R^5, R^6 and R^7, independently of one another, stand for hydrogen, halogen or C_{1-6} alkoxy or C_{1-6} alkyl that is unsubstituted or optionally substituted in one or more places with halogen,
or R^5 and R^6 together form the group



R^8, R^9 and R^{10}, independently of one another, stand for hydrogen or C_{1-6} alkyl,

as well as their isomers and salts, have proven especially effective.

Also especially preferred are compounds of general formula I



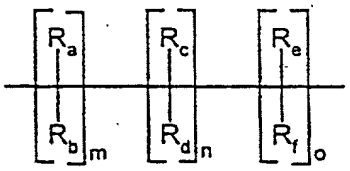
I

in which

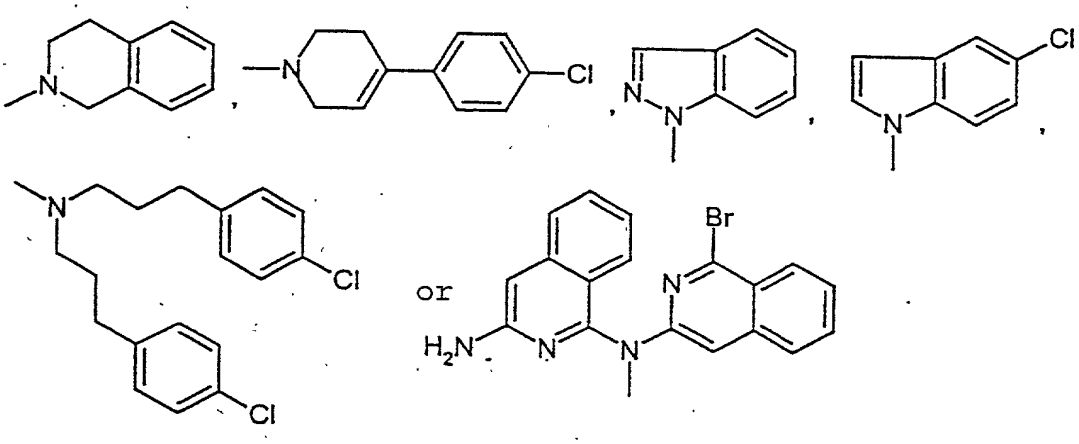
A stands for the group $=NR^2$,

W stands for oxygen, sulfur or two hydrogen atoms,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

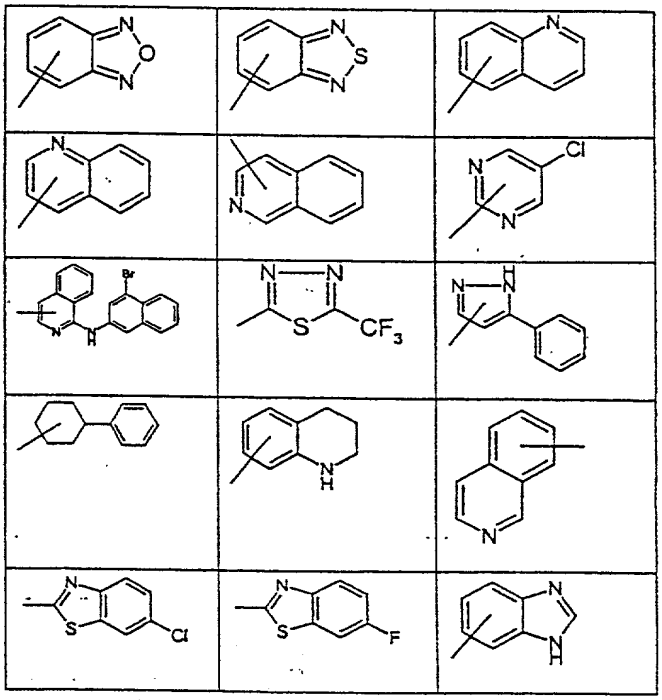
q stands for 1-6,

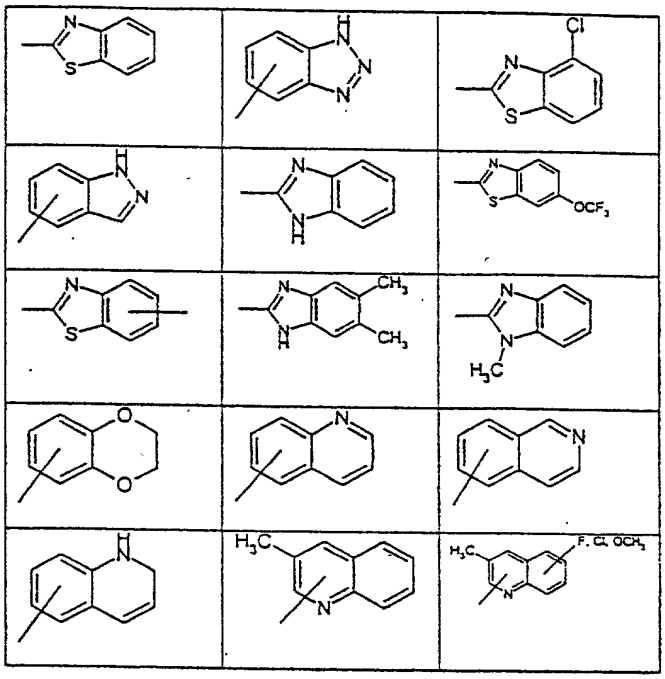
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl, or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, trifluoromethyl, or for the group

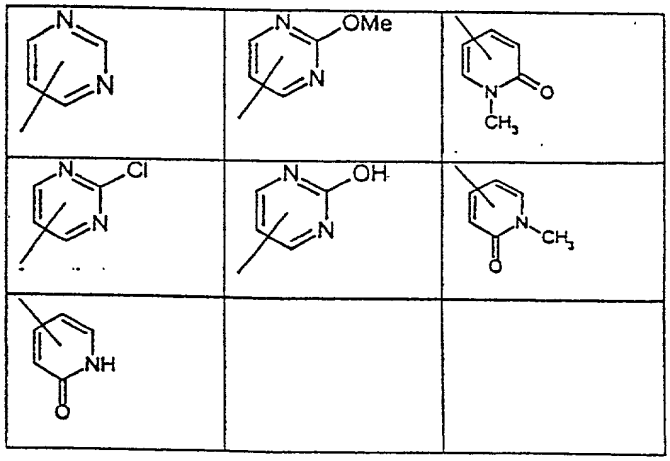




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted with hydroxy, halogen, methyl or methoxy, or the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen or halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

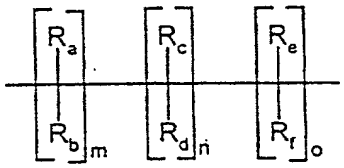
as well as their isomers and salts.

Those compounds of general formula I in which

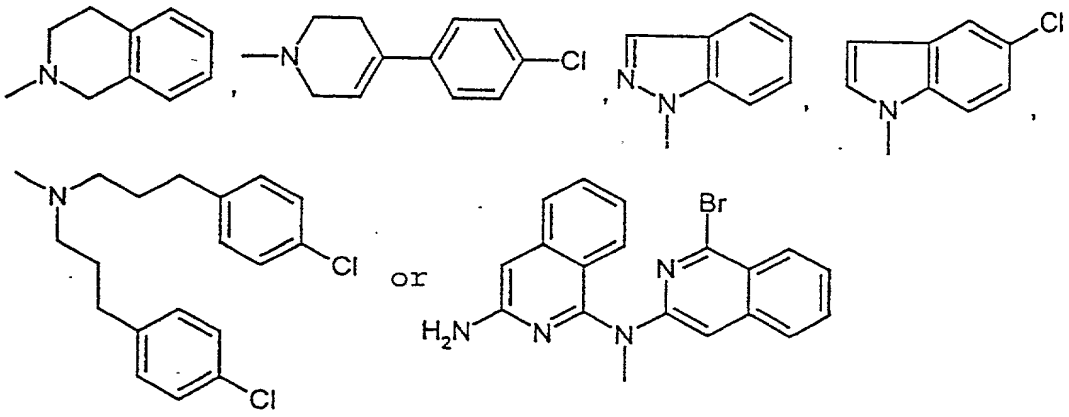
A stands for the group $=NR^2$,

W stands for oxygen,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-$ $(CH_2)_q$- or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

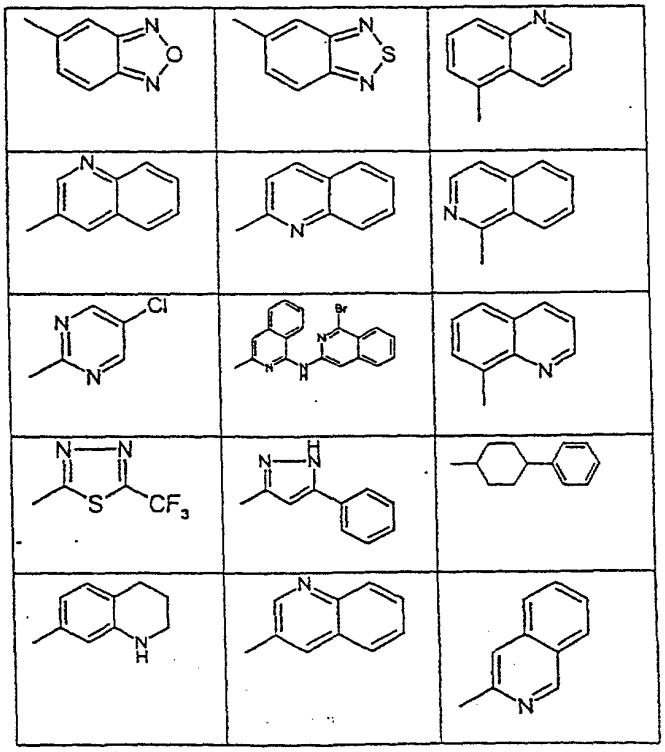
q stands for 1-6,

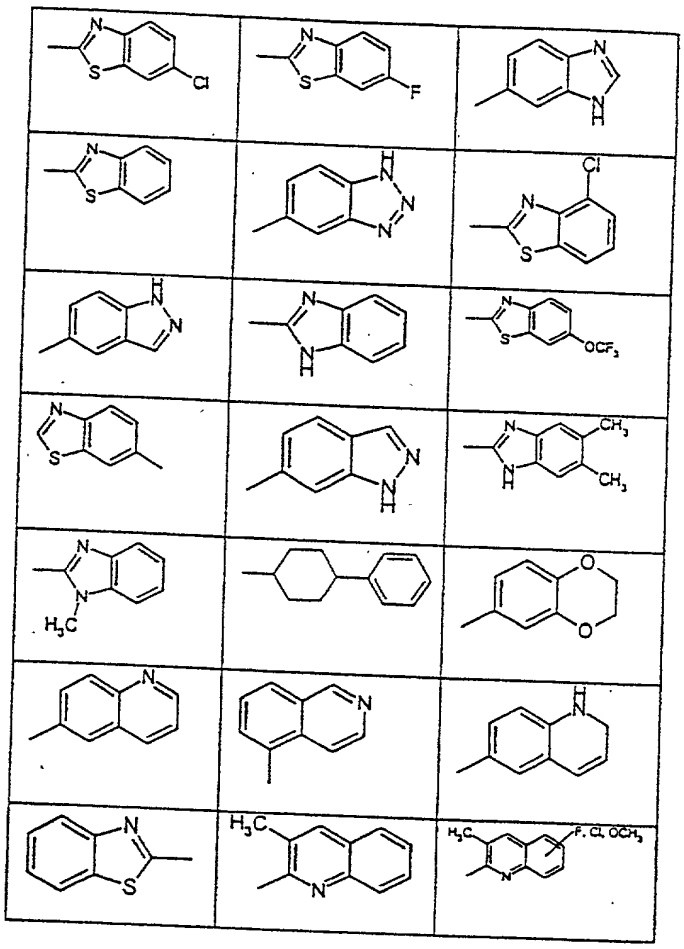
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, trifluoromethyl, or for the group

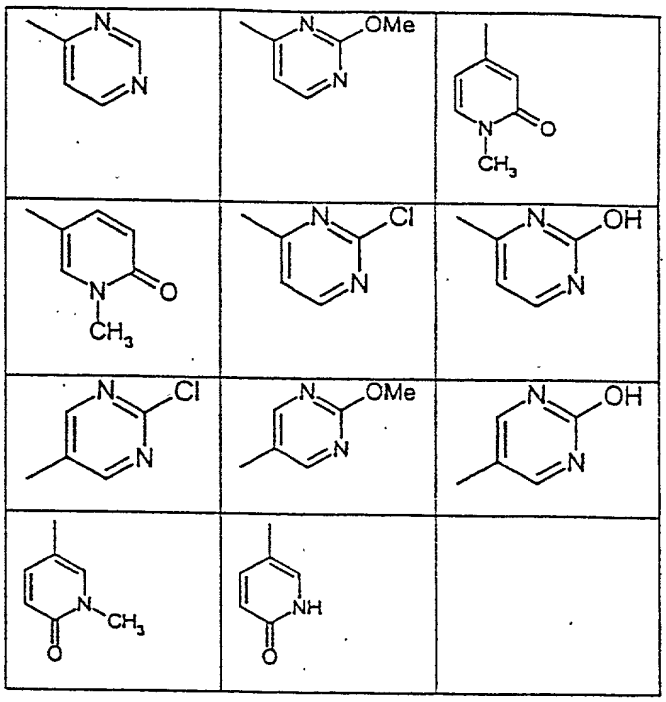




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy, or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

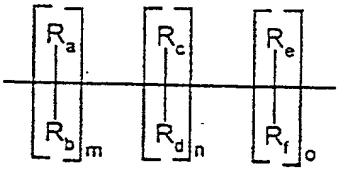
as well as their isomers and salts, have proven quite especially effective.

Those compounds of general formula I in which

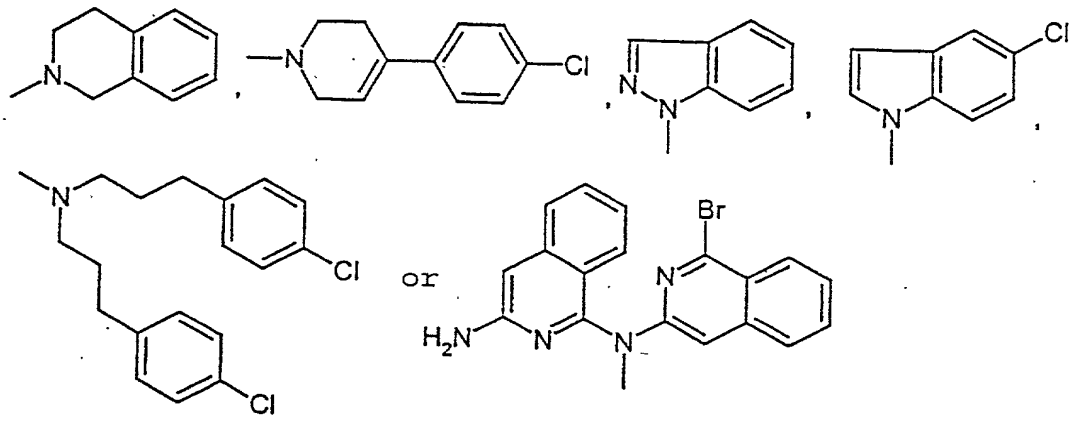
A stands for the group $=NR^2$,

W stands for sulfur,

Z stands for the group $=NR^{10}$, $=N-$, $-N(R^{10})-$ $(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

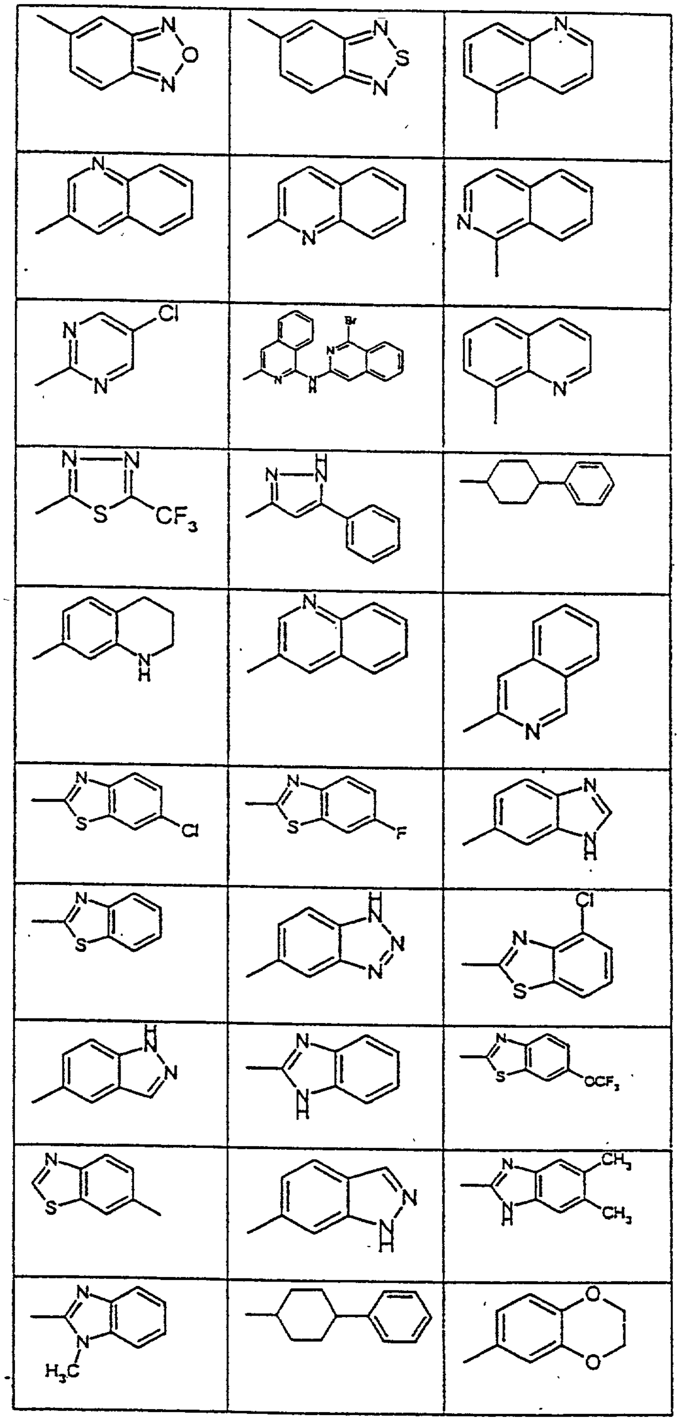
q stands for 1-6,

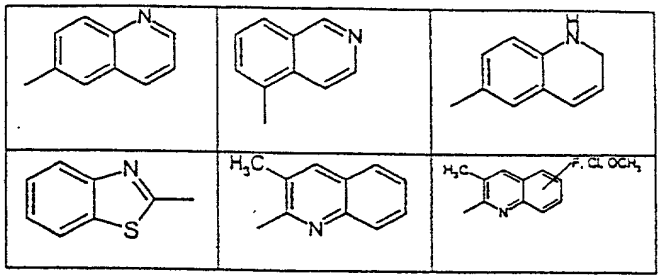
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or $=N-$,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, trifluoromethyl, or for the group

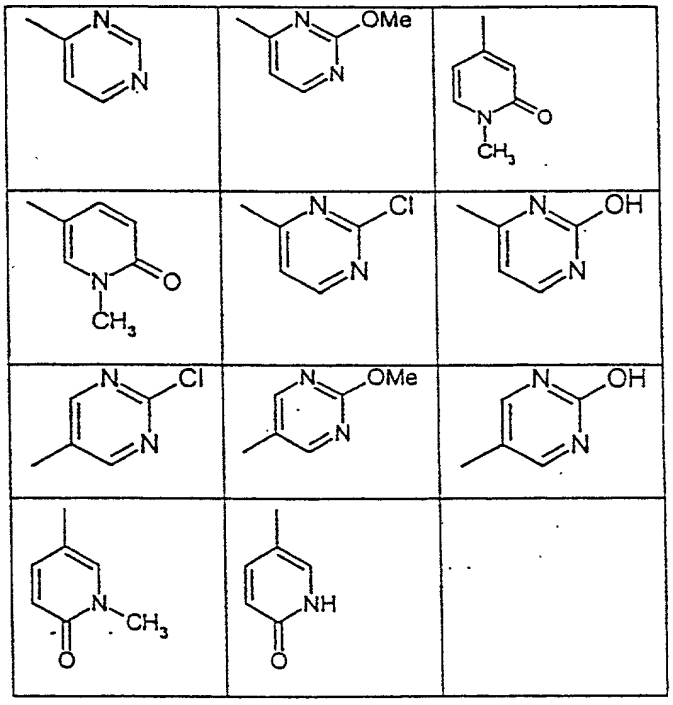




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

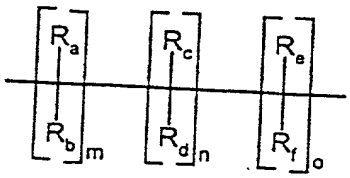
as well as their isomers and salts, have also proven quite especially effective.

Those compounds of general formula I in which

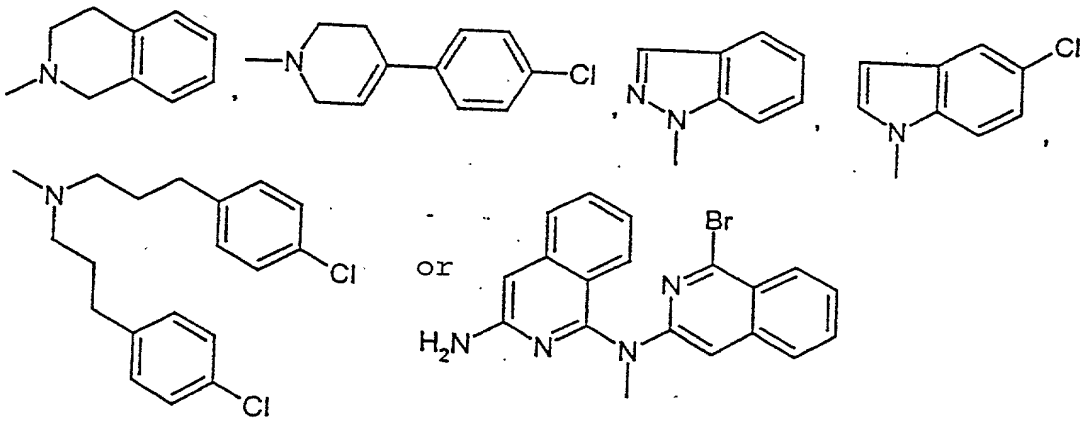
A stands for the group $=NR^2$,

W stands for two hydrogen atoms,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z, and R^1 together form the group



m, n and o stand for 0-3,

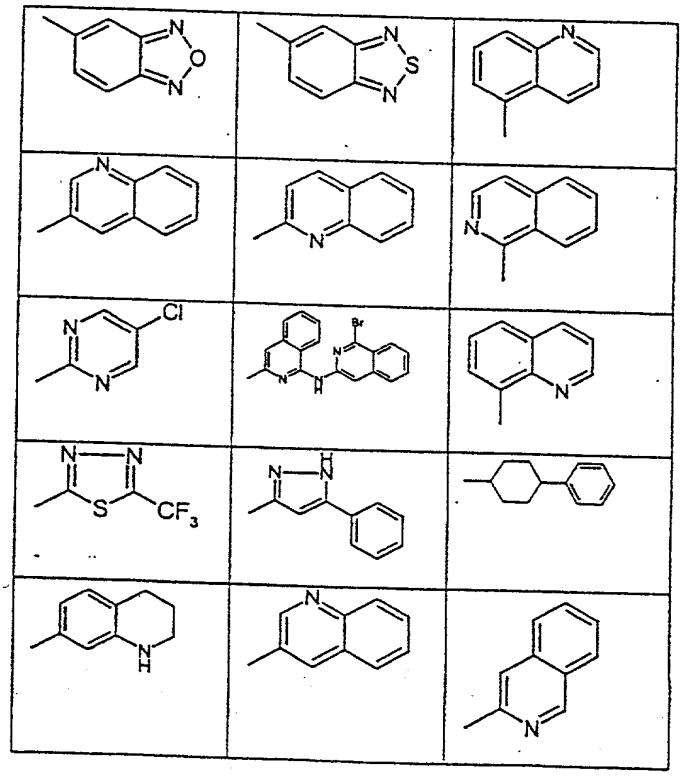
q stands for 1-6,

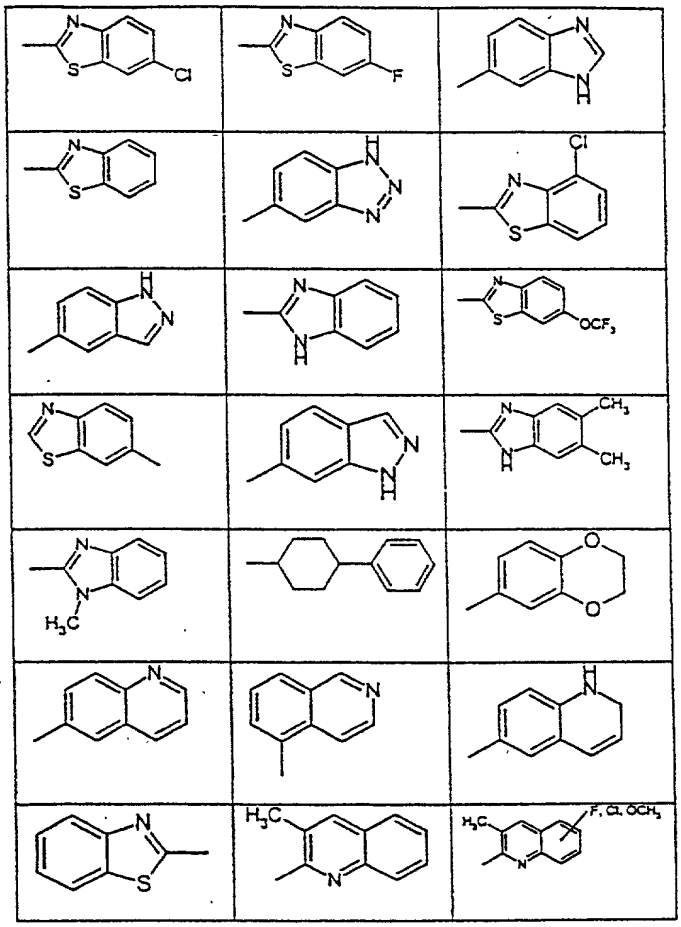
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

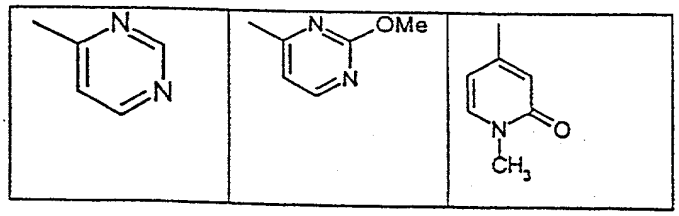


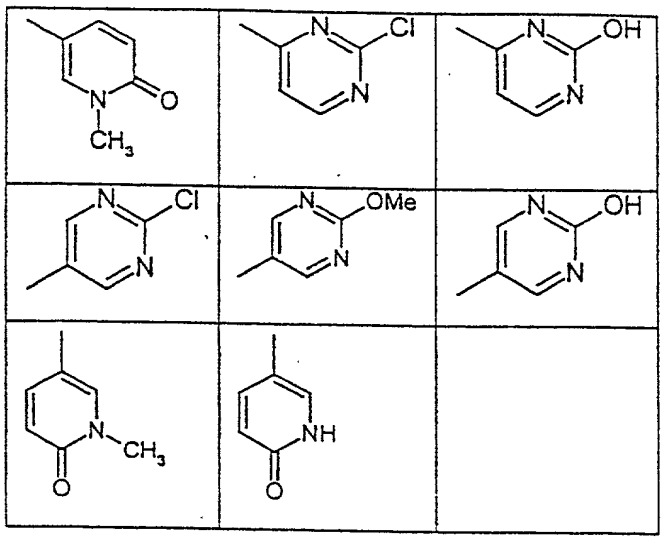


whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group





R^4 and R^7,	independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,
R^5 and R^6,	independently of one another, stand for hydrogen and halogen,
R^9	stands for hydrogen,
R^{10}	stands for hydrogen or methyl,

as well as their isomers and salts, have also proven quite especially effective.

The compounds according to the invention prevent a phosphorylation, i.e., certain tyrosine kinases can be inhibited selectively, whereby the persistent angiogenesis can be stopped. Thus, for example, the growth and the propagation of tumors is suppressed.

The compounds of general formula I according to the invention also include the possible tautomeric forms and comprise

the E- or Z-isomers, or, if a chiral center is present, also the racemates and enantiomers.

The compounds of formula I and their physiologically compatible salts can be used based on their inhibitory activity relative to the phosphorylation of the VEGF receptor as a pharmaceutical agent. Based on their profile of action, the compounds according to the invention are suitable for the treatment of diseases that are caused by persistent angiogenesis.

Since the compounds of formula I are identified as inhibitors of the tyrosine kinases KDR and FLT, they are suitable in particular for treatment of those diseases that are caused by the persistent angiogenesis that is triggered by the VEGF receptor or an increase of vascular permeability.

The subject of this invention is also the use of compounds according to the invention as inhibitors of the tyrosine kinases KDR and FLT.

The subjects of this invention are thus also pharmaceutical agents for the treatment of tumors.

The compounds according to the invention can be used either alone or in a formulation as pharmaceutical agents for the treatment of psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as

cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis and injuries to the nerve tissue.

The compounds according to the invention can also be used in inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

In the treatment of injuries to the nerve tissue, a quick scar formation at the injury sites can be prevented with the compounds according to the invention, i.e., scars are prevented from forming before the axons are reconnected to one another. Reconstruction of the nerve connections thus would be facilitated.

The ascites formation in patients also can be suppressed with the compounds according to the invention. The VEGF-induced edemas can also be suppressed.

Such pharmaceutical agents, their formulations and uses are also the subject of this invention.

The invention also relates to the use of the compounds of general formula I, for the production of a pharmaceutical agent for treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, inhibition of the

reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

To use the compounds of formula I as pharmaceutical agents, the latter are brought into the form of a pharmaceutical preparation, which in addition to the active ingredient for enteral or parenteral administration contains suitable pharmaceutical, organic or inorganic inert support media, such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. The pharmaceutical preparations can be present in solid form, for example as tablets, coated tablets, suppositories, capsules or in liquid form, for example as solutions, suspensions or emulsions. Moreover, they optionally contain adjuvants such as preservatives, stabilizers, wetting agents or emulsifiers, salts for changing osmotic pressure or buffers.

For parenteral use, in particular injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil, are suitable.

As vehicle systems, surface-active adjuvants, such as salts of bile acids or animal or plant phospholipids, but also mixtures thereof as well as liposomes or components thereof can also be used.

For oral use, especially tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binders, such as, for example, lactose, corn or potato starch, are suitable. The

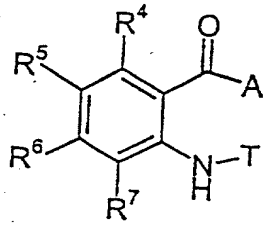
application can also be carried out in liquid form, such as, for example, as juice, to which optionally a sweetener is added.

The dosage of the active ingredients can vary depending on the method of administration, age and weight of the patient, type and severity of the disease that is to be treated, and similar factors. The daily dose is 0.5-1000 mg, preferably 50-200 mg, whereby the dose can be given as a single dose to be administered once or subdivided into 2 or more daily doses.

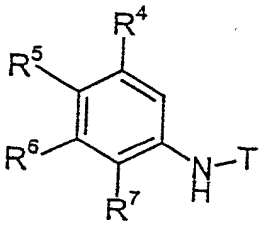
The above-described formulations and forms for dispensing are also the subject of this invention.

The production of the compounds according to the invention is carried out according to methods that are known in the art. For example, compounds of formula I are obtained in that

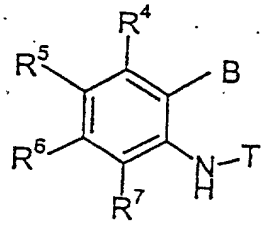
a) A compound of formula II



II



III



IV

in which R^4 to R^7 have the above meaning and T is H or a protective group and A is halogen or OR^{13}, whereby R^{13} means a hydrogen atom, C_{1-4} alkyl or C_{1-4} acyl, or a ring connects with T, first alkylates N and then converts COA into an amide and then

optionally protective groups are cleaved or first converted into the amide and then N-alkylated, or

b) A compound of formula III in which R^4 to R^7 have the above meaning and T means H or a protective group, is in orthometallated form, and then is converted into an amide by being caught with an electrophile, then the protective group is cleaved, and the amino group is alkylated, or

c) A compound of formula IV in which R^4 to R^7 have the above meaning, and T means H or a protective group and B means halogen or O-filtrate, O-tosylate or O-mesylate, is converted into an amide, then the protective group is cleaved off, and the amino group is alkylated.

The sequence of the steps can be reversed in all three cases.

The amide formation is carried out according to methods that are known in the literature.

For amide formation, a start can be made from a corresponding ester. The ester is reacted according to J. Org. Chem. **1995**, 8414 with aluminum trimethyl and the corresponding amine in solvents, such as toluene, at temperatures of 0°C up to the boiling point of the solvent. This method can also be used in unprotected anthranilic acid esters. If the molecule contains two ester groups, both are converted into the same amide.

When nitriles are used instead of ester, amidines are obtained under analogous conditions.

For amide formation, however, all processes that are known from peptide chemistry are also available. For example, the corresponding acid can be reacted in aprotic polar solvents, such as, for example, dimethylformamide on an activated acid derivative, that can be obtained, for example, with hydroxybenzotriazole and a carbodiimide such as, for example, diisopropylcarbodiimide or else with preformed reagents, such as, for example, HATU (Chem. Comm. **1994**, 201) or BTU, at temperatures of between 0°C and the boiling point of the solvent, preferably at 80°C with the amine at HATU preferably at room temperature. These methods can also be used in the unprotected anthranilic acids. For amide formation, the process can also be used on the mixed acid anhydride, imidazolide or azide. A prior protection of the amino group, for example as amide, is not necessary in all cases, but can affect the reaction advantageously. Isatoic acid anhydrides, in which the protection of the amino group and the activation of the acidic function are present at the same time, are a special starting material.

If the amine is already converted into the BOC-protected compound, the ortho-position can be metallated by reaction with organometallic compounds, such as, for example, n-butyllithium, and then caught with isocyanates or isothiocyanates to form the anthranilamides or anthranilthioamides. A bromine or iodine substituent in this ortho-position facilitates the ortho-metallation by halogen-metal exchange. As solvents, ethers such as diethyl ether or tetrahydrofuran or hydrocarbon such as hexane, but also mixtures thereof, are suitable. The addition of

complexing agents, such as tetramethylethylenediamine (TMEDA) is advantageous. The temperatures vary between -78°C and room temperature. The cleavage of the BOC-amides is carried out by treatment with acids, such as trifluoroacetic acid without solvent, or in solvents, such as methylene chloride, at temperatures of 0°C up to the boiling point of the solvent or with aqueous hydrochloric acid, preferably 1N hydrochloric acid, in solvents such as ethanol or dioxane at temperatures from room temperature up to the boiling point of the solvent.

The amide group can also be introduced by carbonylation, however. To this end, a start is made from the corresponding compounds of formula IV (o-iodine, o-bromine or o-triflyloxyanilines), which are reacted with carbon monoxide at normal pressure or else increased pressure and an amine in the presence of transition metal catalysts, such as, for example, palladium(II) chloride or palladium(II) acetate or else palladium tetrakis triphenylphosphine in solvents such as dimethylformamide. The addition of a ligand such as triphenylphosphine and the addition of a base such as tributylamine can be advantageous (see, for example, J. Org. Chem. **1974**, 3327; J. Org. Chem. **1996**, 7482; Synth. Comm. **1997**, 367; Tetr. Lett **1998**, 2835).

If various amide groups are to be introduced into the molecule, the second ester group must be introduced into the molecule, for example, after the production of the first amide group, and then must be amidated, or there is a molecule in which

one group is present as ester and the other as acid, and the two groups are amidated in succession according to various methods.

Thioamides can be obtained from the anthranilamides by reaction with diphosphadithianes according to Bull Soc. Chim. Belg. **87**, 229, 1978 or by reaction with phosphorus pentasulfide in solvents such as pyridine or else without solvent at temperatures of 0°C to 200°C.

As electron-rich aromatic compounds, the products can also be subjected to electrophilic aromatic substitutions. The substitution is then carried out in the ortho- or para-position to form the amino group or one of the amino groups. It can thus be acylated by Friedel-Crafts acylation with acid chlorides in the presence of Friedel-Crafts catalysts, such as, for example, aluminum trichloride in solvents such as nitromethane, carbon disulfide, methylene chloride or nitrobenzene at temperatures of between 0°C and the boiling point of the solvent, preferably at room temperature.

One or more nitro groups can be introduced according to processes that are known in the literature, for example, by nitrating acid, various concentrated nitric acids without solvent or by metal nitrates, such as, for example, copper(II) nitrate or iron(III) nitrate in polar solvents, such as ethanol or glacial acetic acid or else in acetic anhydride.

The introduction of the halogens is carried out according to processes that are known in the literature, e.g., by reaction with bromine, N-bromine, or N-iodosuccinimide or urotropin hydrotribromide in polar solvents, such as tetrahydrofuran,

acetonitrile, methylene chloride, glacial acetic acid or dimethylformamide.

The reduction of the nitro group is performed in polar solvents at room temperature or elevated temperature. As catalysts for the reduction, metals such as Raney nickel or noble metal catalysts such as palladium or platinum or else palladium hydroxide optionally on vehicles are suitable. Instead of hydrogen, for example, ammonium formate, cyclohexene or hydrazine can also be used in a known way. Reducing agents such as tin(II) chloride or titanium(III) chloride can also be used, such as complex metal hydrides, optionally in the presence of heavy metal salts. Iron can also be used as a reducing agent. The reaction is then performed in the presence of an acid, such as, e.g., acetic acid or ammonium chloride, optionally with the addition of a solvent, such as, for example, water, methanol, etc. In the case of extended reaction time, acylation of the amino group can occur in this variant.

If an alkylation of an amino group is desired, alkylation can be done according to commonly used methods -- for example with alkyl halides -- or according to the Mitsunobu variant by reaction with an alcohol in the presence of, for example, triphenylphosphine and azodicarboxylic acid ester. The amine can also be subjected to reductive alkylation with aldehydes or ketones, whereby it is reacted in the presence of a reducing agent, such as, for example, sodium cyanoborohydride in a suitable inert solvent, such as, for example, ethanol, at temperatures of 0°C up to the boiling point of the solvent. If a

start is made from a primary amino group, a reaction can be carried out optionally in succession with two different carbonyl compounds, whereby mixed derivatives are obtained [literature, e.g., Verardo et al. Synthesis (1993), 121; Synthesis (1991), 447; Kawaguchi, Synthesis (1985), 701; Micovic et al. Synthesis (1991), 1043].

It may be advantageous to form the Schiff base first by reaction of the aldehyde with the amine in solvents such as ethanol or methanol, optionally with the addition of adjuvants such as glacial acetic acid, and then to add only reducing agent, such as, e.g., sodium cyanoborohydride.

The hydrogenation of alkene or alkine groups in the molecule is carried out in the usual way by, for example, catalytically activated hydrogen. As catalysts, heavy metals such as palladium or platinum, optionally on a vehicle or Raney nickel, can be used. As solvents, alcohols, such as, e.g., ethanol, are suitable. The procedure is performed at temperatures of 0°C up to the boiling point of the solvent and at pressures of up to 20 bar, but preferably at room temperature and normal pressure. By using catalysts, such as, for example, a Lindlar catalyst, triple bonds can be partially hydrogenated into double bonds, whereby preferably the Z-form is produced.

The acylation of an amino group is carried out in the usual way with, for example, an acid halide or acid anhydride, optionally in the presence of a base such as dimethylaminopyridine in solvents such as methylene chloride, tetrahydrofuran or pyridine, according to the Schotten-Baumann

variant in aqueous solution at weakly alkaline pH or by reaction with an anhydride in glacial acetic acid.

The introduction of the halogens chlorine, bromine, iodine or the azido group via an amino group can also be carried out, for example, according to Sandmeyer, by the diazonium salts that are formed as intermediate products with nitrites being reacted with copper(I) chloride or copper(I) bromide in the presence of the corresponding acid such as hydrochloric acid or hydrobromic acid or with potassium iodide.

If an organic nitrite is used, the halogens can be introduced into a solvent, such as, for example, dimethylformamide, e.g., by addition of methylene iodide or tetrabromomethane. The removal of the amino group can be achieved either by reaction with an organic nitrite in tetrahydrofuran or by diazotization and reductive boiling down of the diazonium salt with, for example, phosphorous acid optionally with the addition of copper(I) oxide.

The introduction of fluorine can be carried out by, for example, Balz-Schiemann reaction of the diazonium tetrafluoroborate or according to J. Fluor. Chem. **76**, 1996, 59-62 by diazotization in the presence of HFxpyridine and subsequent boiling-down optionally in the presence of a fluoride ion source, such as, e.g., tetrabutylammonium fluoride.

The introduction of the azido group can be carried out after diazotization by reaction with sodium azide at room temperature.

Ether cleavages are performed according to processes that are common in the literature. In this case, a selective cleavage

can be achieved also in several groups that are present in the molecule. In this case, the ether is treated with, for example, boron tribromide in solvents such as dichloromethane at temperatures of between -100°C up to the boiling point of the solvent, preferably at -78°C. It is also possible, however, to cleave the ether by sodium thiomethylate in solvents such as dimethylformamide. The temperature can lie between room temperature and the boiling point of the solvent, preferably at 150°C.

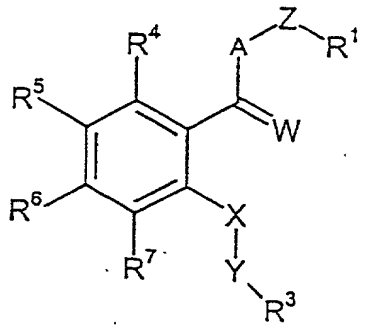
The N- or O-alkylation of amides such as the pyrid-2-one or 2-hydroxypyridine can be carried out according to methods that are known in the literature. An N-alkylation thus can be achieved with bases such as sodium hydride or potassium carbonate in solvents such as dimethylformamide and alkylation with alkyl halides such as methyl iodide. An O-alkylation with bases such as silver carbonate in solvents such as tetrahydrofuran or toluene or preferably mixtures thereof with alkyl halides, such as methyl iodide. An O-alkylation is also obtained during conversion with trialkyloxonium tetrafluoroborate in inert solvents such as methylene chloride. Mixtures of N- and O-alkyl derivatives are obtained in the reaction with diazomethane or trimethylsilyldiazomethane in solvents such as methanol or toluene, preferably in mixtures thereof at temperatures up to the boiling point of the solvent, but preferably at room temperature. The methods make possible a selective alkylation of the pyridone relative to the benzoic acid amide.

According to commonly used methods, such as, for example, crystallization, chromatography or salt formation, the isomer mixtures can be separated into enantiomers or E/Z-isomers.

The production of the salts is carried out in the usual way, by a solution of the compound of formula I being mixed with the equivalent amount or an excess of a base or acid, which optionally is in solution, and the precipitate being separated or the solution being worked up in the usual way.

If the production of the starting compounds is not described, the latter are known or can be produced analogously to known compounds or processes that are described here.

Also subjects of this invention are the isatoic acid derivatives of general formula V



V,

in which R^3-R^7, X, Y and W have the meanings that are described in general formula I and in which A stands for the group $=NR^2$ or oxygen, and Z and R^1 together form a =C=O group that is bonded to X, as well as their isomers and salts, as valuable intermediate

products for the production of the compounds of general formula I according to the invention.

Especially valuable are those intermediate products of general formula V in which

A and W	stand for oxygen,
Z and R'	together form a =C=O group that is bonded to X,
X	stands for the group $=NR^9$ or =N-,
Y	stands for the group $-CH_2-$,
R^3	stands for pyridyl or phenyl or 1,2,3,4-tetrahydronaphthyl that is substituted by hydroxy, bromine, methyl or methoxy,
R^5 and R^6	stand for hydrogen, chlorine, methyl, methoxy or trifluoromethyl,
R^4 and R^7	stand for hydrogen,
R^9	stands for hydrogen,

as well as their isomers and salts.

The intermediate products are partially active on their own and can thus also be used for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, inhibition of the

reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

The examples below explain the production of the compounds according to the invention without limiting the scope of the claimed compounds to these examples.

Example 1.0

Production of N-(4-Pyridylmethyl)-anthranilic acid methyl ester

Under nitrogen atmosphere, a mixture of 7.5 g of anthranilic acid methyl ester and 8.6 g of pyridine-4-carbaldehyde in 300 ml of methanol is mixed with 3 ml of acetic acid and stirred for 12 hours at room temperature. Then, the reaction mixture is mixed with 5.7 g of sodium cyanoborohydride (85%) and stirred for another 3 hours at room temperature. After this time, 1.14 g of sodium cyanoborohydride (85%) is added again and stirred for another 12 hours at room temperature. The reaction mixture is concentrated by evaporation. The residue is taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. The dried organic phase is concentrated by evaporation, and the residue is purified with use of column chromatography on silica gel with use of hexane/ethyl acetate (1+1).

10.2 g of the title compound with a melting point of 85.6°C is obtained.

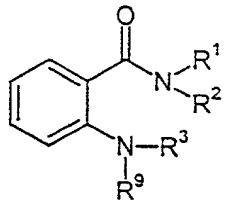
Example 2.0

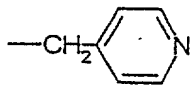
Production of N-(3-phenylprop-1-yl)-N2-(4-pyridylmethyl)-anthranilic acid amide

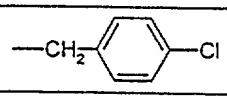
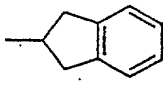
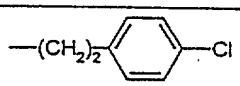
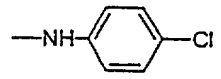
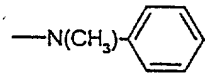
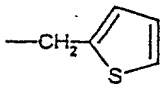
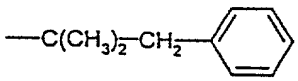
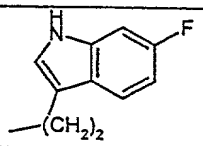
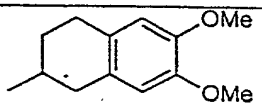
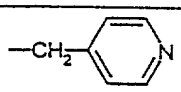
242 mg of N-(4-pyridylmethyl)-anthranilic acid methyl ester is introduced into 3.5 ml of toluene, mixed with 202 mg of 3-phenylpropylamine and quickly mixed at 0°C with 0.75 ml of a 2 molar solution of trimethylaluminum in toluene. The reaction mixture is then heated for 1 hour at room temperature and then refluxed for 1 hour. After cooling, the reaction mixture is added to saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic phase is washed, dried, filtered and concentrated by evaporation in a vacuum. The residue is then recrystallized from ethyl acetate.

265 mg of the title compound with a melting point of 117.4°C is obtained.

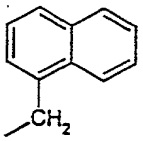
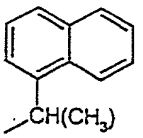
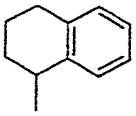
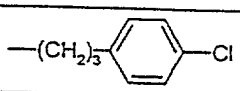
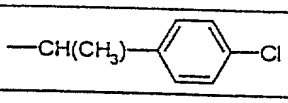
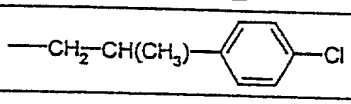
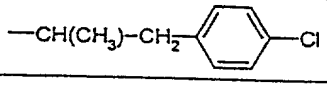
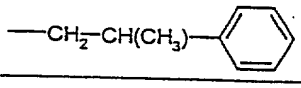
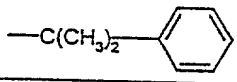
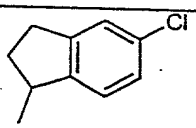
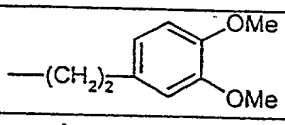
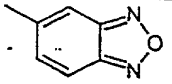
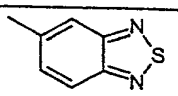
Produced similarly to Example 2.0 are also the following compounds:



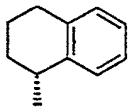
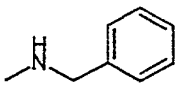
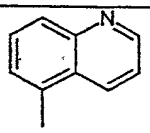
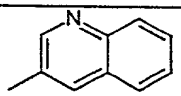
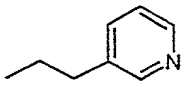
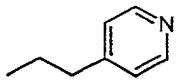
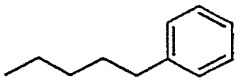
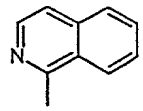
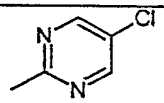
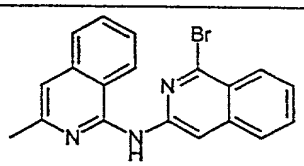
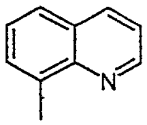
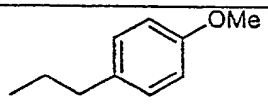
R^2, R^9 = H R^3 = 

Beispiel	R^1	Schmelzpunkt °C
2.1		133,4
2.2		152,8
2.3		107,7
2.4		Öl
2.5		123-124
2.6		88,1
2.7		114,5
2.8		170,5
2,9		65,5
2.10		Öl

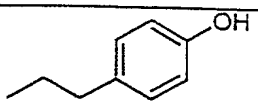
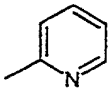
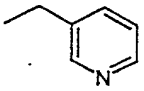
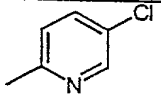
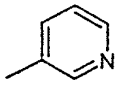
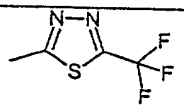
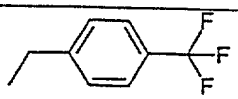
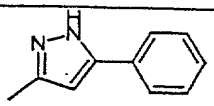
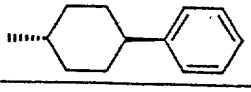
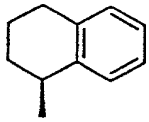
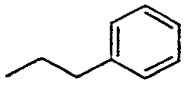
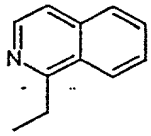
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	Schmelzpunkt °C
2.11		119
2.12		156,2
2.13		121,7
2.14		Öl
2.15		166,4
2.16		Öl
2.17		132,9
2.18		Öl
2.19		133,8
2.20		Öl
2.21		Öl
2.22		Öl
2.23		Öl

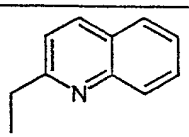
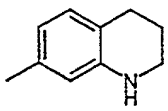
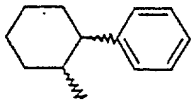
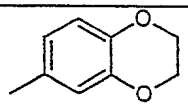
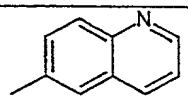
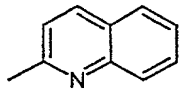
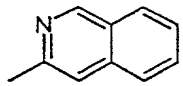
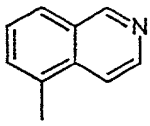
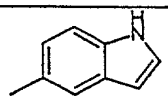
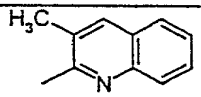
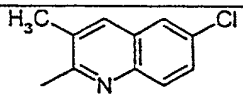
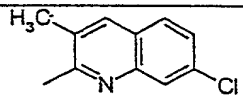
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	Schmelzpunkt °C
2.24		Öl
2.25		Öl
2.26		129,7
2.27		182,4
2.28		105-106
2.29		94-95
2.30		Öl
2.31		152,3
2.32		173-175
2.33		190-192
2.34		176,4
2.35		110-111

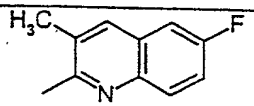
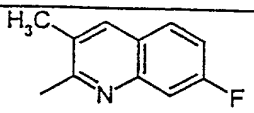
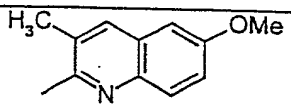
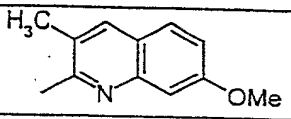
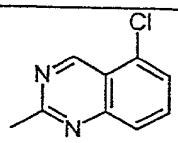
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	Schmelzpunkt °C
2.36		157-159
2.37		118-120
2.38		119-121
2.39		130-132
2.40		128-129
2.41		172-174
2.42		155-156
2.43		167
2.44		178,8
2.45		Öl
2.46		Öl
2.47		140-142

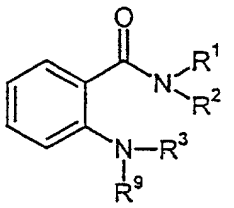
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	Schmelzpunkt °C
2.48		116-118
2.49		96-99
2.50		169,4
2.51		145-147
2.52		141,1
2.53		160,6
2.54		134,3
2.55		Öl
2.56		157,5
2.76		195
2.77		198
2.78		192

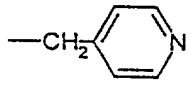
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

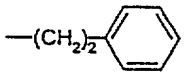
Beispiel	R^1	Schmelzpunkt °C
2.79		215
2.80		161
2.81		169
2.82		132
2.83		194

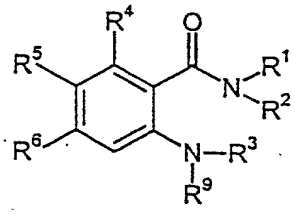
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point



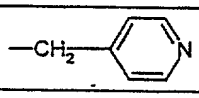
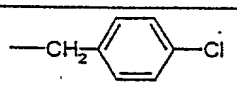
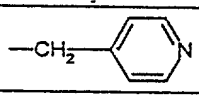
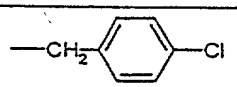
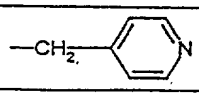
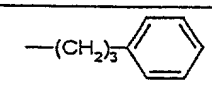
$R^2 = -CH_3$
$R^9 = H$

$R^3 =$ 

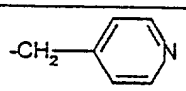
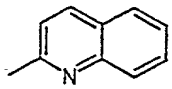
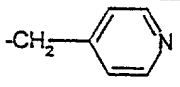
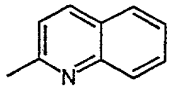
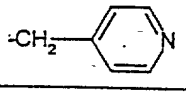
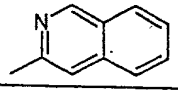
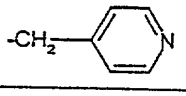
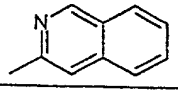
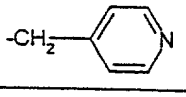
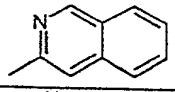
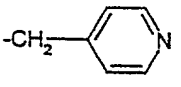
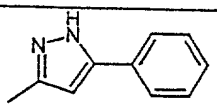
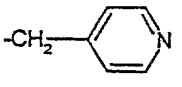
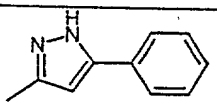
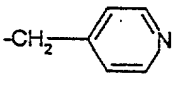
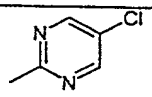
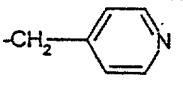
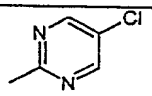
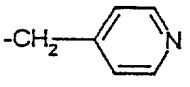
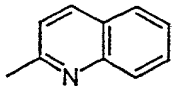
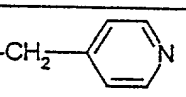
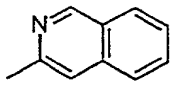
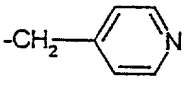
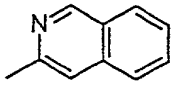
Beispiel	R^1	Schmelzpunkt °C
2.57		Öl



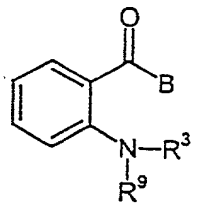
$R^2, R^9 = H$

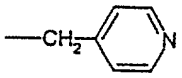
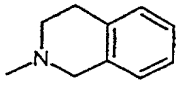
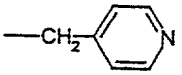
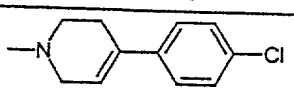
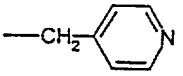
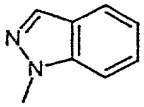
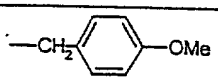
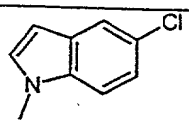
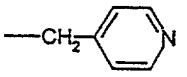
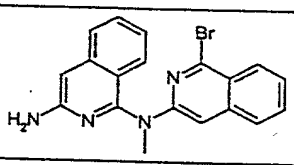
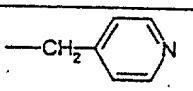
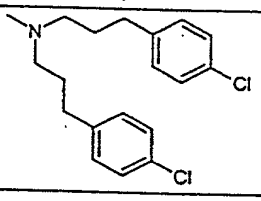
Beispiel	R^6	R^5	R^4	R^3	R^1	Schmelzpunkt °C
2.58	H	Cl	H			Öl
2.59	H	H	Cl			135-136
2.60	H	Cl	H			Öl

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^6	R^5	R^4	R^3	R^1	Schmelzpunkt °C
2.61	H	H	Cl			193-195
2.62	H	Cl	H			186,8
2.63	H	F	H			Öl
2.64	H	Cl	H			Öl
2.65	F	H	H			168,6
2.66	H	Cl	H			Öl
2.67	H	F	H			Öl
2.68	H	Cl	H			Öl
2.69	H	F	H			Öl
2.84	Cl	H	H			165.6
2.85	H	H	F			Harz
2.86	F	F	H			206.0

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point



Beispiel	R^9	R^3	B	Schmelzpunkt °C
2.70	H			Öl
2.71	H			136,8
2.72	H			Öl
2.73	H			Öl
2.74	H			Öl
2.75	H			Öl

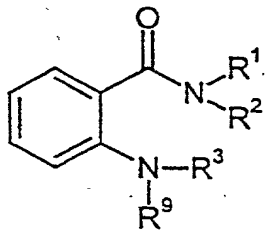
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Example 3.0

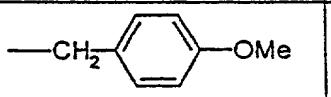
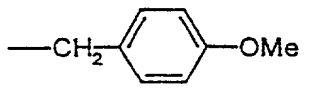
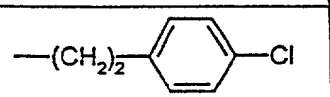
Production of N-(4-chlorobenzyl)-N2-(4-methoxybenzyl)anthranilamide

425 mg of N-(4-methoxybenzyl)isatoic acid anhydride is dissolved in 20 ml of tetrahydrofuran p.A., mixed with 234 mg of 4-chlorobenzylamine and refluxed for 4 hours. The reaction solution is concentrated by evaporation in a vacuum, taken up in ethyl acetate, washed, dried, filtered and concentrated by evaporation in a vacuum. The residue is recrystallized from ethyl alcohol. The title compound with a melting point of 130.5°C is obtained.

Similarly produced are also the following compounds:



$R^2, R^9 = H$

Beispiel	R^3	R^1	Schmelzpunkt °C
3.1			100,7
3.2			110,5

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Example 4.0

Production of N-[2-(4-chlorophenyl)ethyl]-N2-(4-hydroxybenzyl)anthranilamide

71 mg of N-[2-(4-chlorophenyl)ethyl]-N2-(4-methoxybenzyl)anthranilamide is dissolved under nitrogen atmosphere in 2 ml of absolute dimethylformamide and mixed with 76 mg of sodium thiomethylate. The reaction mixture is refluxed for 1.5 hours. After cooling, it is mixed with 30 ml of water and then extracted with ethyl acetate. The organic phase is washed, dried, filtered and evaporated to the dry state in a vacuum. The residue is chromatographed on silica gel with hexane + ethyl acetate (7 + 3) as an eluant.

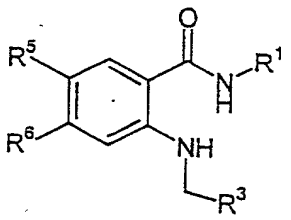
23 mg of the title compound with a melting point of 103-105°C is obtained.

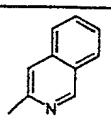
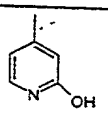
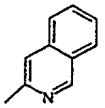
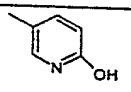
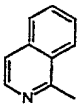
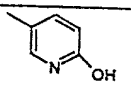
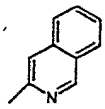
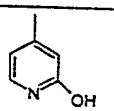
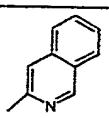
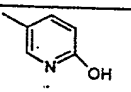
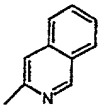
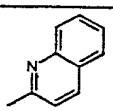
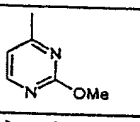
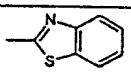
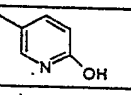
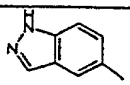
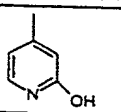
Example 5.0

Production of 2-[(-2-chloropyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide

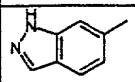
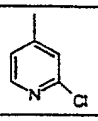
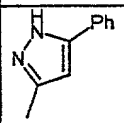
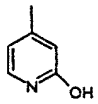
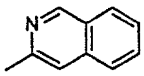
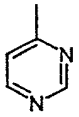
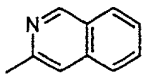
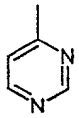
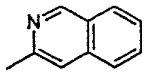
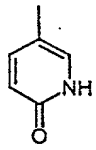
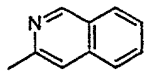
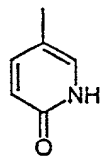
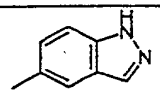
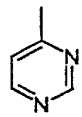
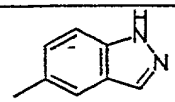
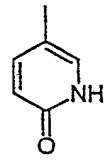
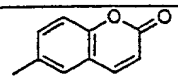
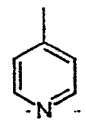
300 mg of 2-[amino]-N-(isoquinolin-3-yl)benzoic acid amide is mixed in 6 ml of methanol with 0.06 ml of glacial acetic acid and 523 mg of a 39% solution of 2-chloro-4-pyridine carbaldehyde in methylene chloride and ethyl acetate, and it is stirred for 20 hours at room temperature under argon. Then, 96 mg of sodium cyanoborohydride is added, and it is stirred for 6 hours at room temperature. After concentration by evaporation in a vacuum, the residue is taken up in 30 ml of a dilute solution of sodium bicarbonate in water and extracted with ethyl acetate. The ethyl acetate phase is washed with water, dried, filtered and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate as an eluant. After the corresponding fractions are combined and concentrated by evaporation, 56 mg of 2-[(-2-chloropyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide is obtained.

Similarly produced are also the following compounds:



Beispiel	R^1	R^3	R^6	R^5	Schmelzpunkt °C
5.1			H	H	Öl
5.2			H	H	238.3
5.3			F	H	Öl
5.4			H	F	Öl
5.5			Cl	H	Öl
5.6			H	H	171.8
5.7			H	H	Öl
5.8			F	H	Öl
5.9			H	H	Öl

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	R^3	R^6	R^5	Schmelzpunkt °C
5.10			H	F	Öl
5.11			H	H	Öl
5.12			F	H	Öl
5.13			H	F	156.1
5.14			H	F	Öl
5.15			F	H	Öl
5.16			F	H	238.6
5.17			H	H	Öl
5.18			H	H	Öl

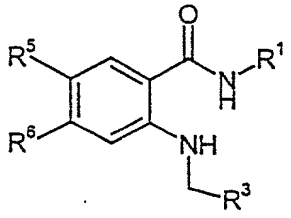
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

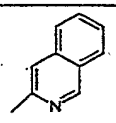
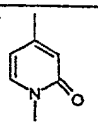
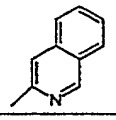
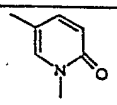
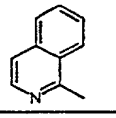
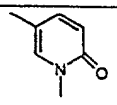
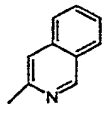
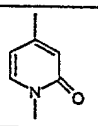
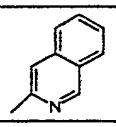
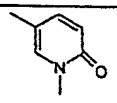
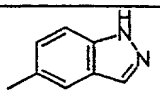
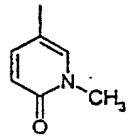
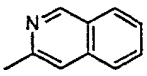
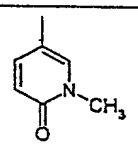
Example 6.0

Production of 2-[[(1,2-dihydro-1-methyl-2-oxopyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide

80 mg of 2-[[(1,2-dihydro-2-oxopyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide in 2 ml of dimethylformamide is mixed under argon with 10 mg of sodium hydride (80%) and heated for 30 minutes to 60°C. Then, 0.015 ml of methyl iodide in 0.5 ml of dimethylformamide is added in drops and heated for 1 hour to 60°C. After cooling, the batch is added to a solution of sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate phase is washed, dried and concentrated by evaporation, and the residue on silica gel with methylene chloride:ethanol = 97:3 as an eluant. 30 mg of 2-[[(1,2-dihydro-1-methyl-2-oxopyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide is obtained.

Similarly produced are also the following compounds:



Beispiel	R^1	R^3	R^6	R^5	Schmelzpunkt °C
6.1			H	H	Öl
6.2			H	H	Öl
6.3			F	H	Öl
6.4			H	F	Öl
6.5			Cl	H	Öl
6.6			H	H	Öl
6.7			H	H	Öl

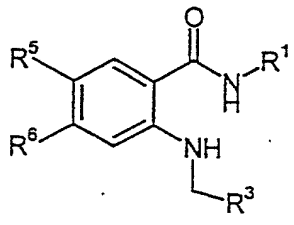
[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

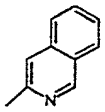
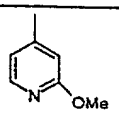
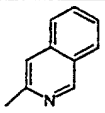
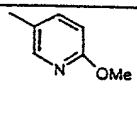
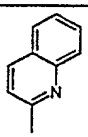
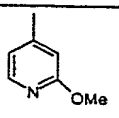
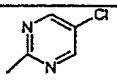
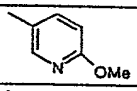
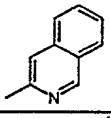
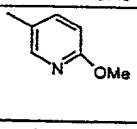
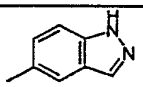
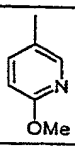
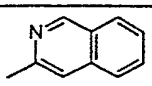
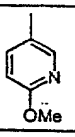
Example 7.0

Production of 2-[(-2-methoxypyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide and 2-[[(1,2-dihydro-1-methyl-2-oxopyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide

130 mg of 2-[[(1,2-dihydro-2-oxopyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide is introduced into 4 ml of a mixture that consists of toluene:methanol = 1:3.5 and mixed with 0.2 ml of a 2-molar solution of trimethylsilyldiazomethane in hexane and stirred for 8 hours at room temperature. After repeated addition of 0.2 ml of trimethylsilyldiazomethane solution and 1 hour of stirring, the batch is evaporated to the dry state and chromatographed on silica gel with methylene chloride:ethanol = 97:3 as an eluant. 20 mg of 2-[(-2-methoxypyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)benzoic acid amide and 10 mg of 2-[[(1,2-dihydro-1-methyl-2-oxopyridin-4-yl)methyl]amino]-N-(isoquinolin-3-yl)-benzoic acid amide are obtained.

Similarly produced are also the following compounds:



Beispiel	R^1	R^3	R^6	R^5	Schmelzpunkt °C
7.1			H	H	Öl
7.2			H	H	Öl
7.3			F	H	Öl
7.4			H	F	Öl
7.5			Cl	H	Öl
7.6			H	H	Öl
7.7			H	H	Öl

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

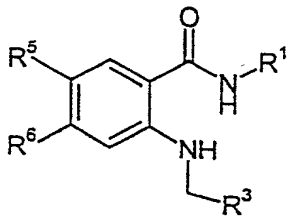
Example 8.0

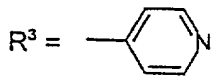
Production of N-(indazol-5-yl) N2-(4-pyridylmethyl)-anthranilic acid amide

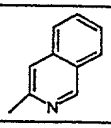
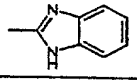
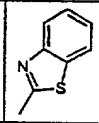
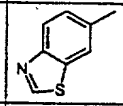
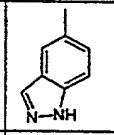
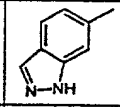
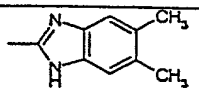
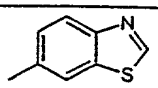
228 mg of N-(4-pyridylmethyl)-anthranilic acid is introduced into 10 ml of dimethylformamide under argon and in a moisture-free environment. 266 mg of 5-aminoindazole, 0.27 ml of methylmorpholine and 456 mg of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) are added. The mixture is then stirred for 4 hours at room temperature. It is then mixed with dilute sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic phases are washed with water, dried, filtered and concentrated by evaporation in a vacuum. The residue is chromatographed on silica gel with ethyl acetate as an eluant.

By absorptive precipitation in acetone, 245 mg of the title compound with a melting point of 209.8°C is obtained.

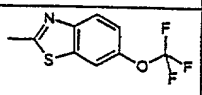
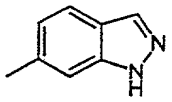
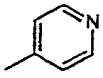
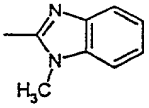
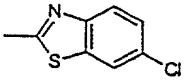
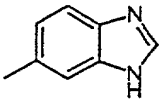
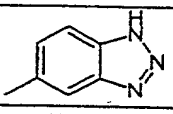
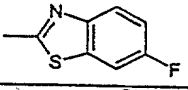
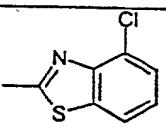
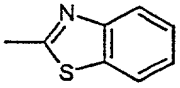
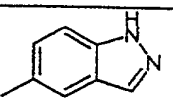
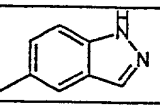
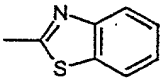
Similarly produced are also the following compounds:



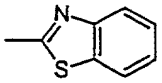
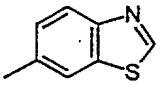


Beispiel	R^1	R^6	R^5	Schmelzpunkt °C
8.1		Cl	H	Öl
8.2		H	H	206
8.3		F	H	Öl
8.4		H	F	58.7
8.5		Cl	H	Öl
8.6		F	H	Öl
8.7		H	H	211,7
8.8		H	H	140.4

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	R^6	R^5	Schmelzpunkt °C
8.9		H	H	188,5
8.10		H	H	258,2
8.11		H	H	152,6
8.12		H	H	199,7
8.13		H	H	178,3
8.14		H	H	243
8.15		H	H	Öl
8.16		H	H	230,4
8.17		H	H	Öl
8.18		H	Cl	235-236
8.19		H	F	236
8.20		H	Cl	228,1
8.21		H	H	Öl

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Beispiel	R^1	R^6	R^5	Schmelzpunkt °C
8.22		H	F	197.6
8.23		H	Cl	59.1

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

The following example explains the production of the intermediate products according to the invention, without limiting the invention to these examples.

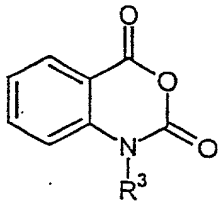
Example 9.0

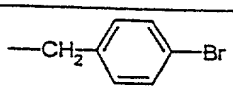
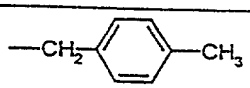
Production of N-(4-methoxybenzyl)isatoic acid anhydride as an intermediate product for the production of the end products according to the invention.

Under nitrogen atmosphere, a solution that consists of 5 g of isatoic acid anhydride and 100 ml of N,N-dimethylacetamide is cooled in an ice bath and mixed in portions with 1.35 g of sodium hydride (oil ~ 60%). The reaction mixture is then stirred for 30 minutes at room temperature and for another 30 minutes at a bath temperature of 60°C. After cooling to room temperature, 5 ml of 4-methoxybenzaldehyde is added in drops while being stirred, and it is stirred overnight at room temperature. The reaction mixture is concentrated by evaporation in a vacuum and poured onto 100 ml of ice/water. The precipitate is separated, taken up in 50 ml of methylene chloride, washed, dried, filtered and concentrated by evaporation in a vacuum. The residue is recrystallized from alcohol.

3.4 g of the title compound with a melting point of 143°C is obtained.

Similarly produced are also the following compounds:



Beispiel	R^3	Schmelzpunkt °C
9.1		Öl
9.2		Öl

[Key:]
Beispiel = Example; Schmelzpunkt = Melting Point

Example 10.0

Production of N-(4-pyridylmethyl)-anthranilic acid as an intermediate product for the production of the end products according to the invention

2 g of N-(4-pyridylmethyl)-anthranilic acid methyl ester is dissolved in 15 ml of methanol, mixed with 16 ml of 1N sodium hydroxide solution and refluxed for 1 hour. After cooling, the methanol is distilled off under vacuum, and the residue is mixed with 20 ml of water and 20 ml of 1N citric acid solution. The crystals are suctioned off, washed with water and dried.

1.7 g of the title compound with a melting point of 208.0°C is obtained.

Example 11.0

Production of N-(indazol-5-yl)-5-chloroanthranilic acid amide as an intermediate product for the production of the end products according to the invention

171 mg of 5-chloroanthranilic acid is introduced into 10 ml of dimethylformamide under argon and in a moisture-free environment and mixed in succession with 253 mg of N-methylmorpholine, 266 mg of 5-aminoindazole and 456 mg of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and stirred for 4 hours at room temperature. After standing overnight, it is mixed with 50 ml of water and extracted with 30 ml of ethyl acetate. The organic phase is washed with water, dried, filtered and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate as an eluant. 266 mg of N-(indazol-5-yl)-5-chloroanthranilic acid amide is obtained.

The following sample applications explain the biological action and use of the compounds according to the invention without limiting the latter to the examples.

Solutions required for the tests

Stock solutions

Stock solution A: 3 mmol of ATP in water, pH 7.0 (-70°C)

Stock solution B: g-33P-ATP 1 mCi/100 µl

Stock solution C: poly-(Glu4Tyr) 10 mg/ml in water

Solution for dilutions

Substrate solvent: 10 mmol of DTT, 10 mmol of manganese chloride, 100 mmol of magnesium chloride

Enzyme solution: 120 mmol of tris/HCl, pH 7.5, 10 µm of sodium vanadium oxide

Sample Application 1

Inhibition of the KDR- and FLT-1 kinase activity in the presence of the compounds according to the invention

In a microtiter plate (without protein binding) that tapers to a point, 10 µl of substrate mixture (10 µl of vol of ATP stock solution A + 25 µCi of g-33P-ATP (about 2.5 µl of stock solution B) + 30 µl of poly-(Glu4Tyr) stock solution C + 1.21 ml of substrate solvent), 10 µl of inhibitor solution (substances that correspond to the dilutions, as a control 3% DMSO in substrate solvent), and 10 µl of enzyme solution (11.25 µg of enzyme stock solution (KDR or FLT-1 kinase) is diluted at 4°C in 1.25 ml of

enzyme solution) are added. It is thoroughly mixed and incubated for 10 minutes at room temperature. Then, 10 μl of stop solution (250 mmol of EDTA, pH 7.0) is added, mixed, and 10 μl of the solution is transferred to a P 81 phosphocellulose filter. Then, it is washed several times in 0.1 M phosphoric acid. The filter paper is dried, coated with Meltilex and measured in a microbeta counter.

The IC50 values are determined from the inhibitor concentration, which is necessary to inhibit the phosphate incorporation to 50% of the uninhibited incorporation after removal of the blank reading (EDTA-stopped reaction).

The results of kinase-inhibition IC50 in μmol are depicted in the following table:

Beispiel-Nr.	VEGFR I (FLT)	VEGFR II (KDR)
2.0	0,05	0,05
2.1	0,01	0,3
2.2	0,1	0,5
2.3	0,02	0,02
2.4	0,02	0,1
2.5	1	10
2.6	0,2	2
2.8	0,5	0,1
2.9	5	1
2.10	3	10
2.11	0,02	0,2
2.12	0,7	3
2.13	0,7	3
2.14	0,5	0,3
2.15	1,0	KH
2.16	0,1	0,2
2.17	0,4	0,5
2.18	0,3	0,5
2.19	>10	>10

[Key:]
Beispiel-Nr. = Example No.

Beispiel-Nr.	VEGFR I (FLT)	VEGFR II (KDR)
2.20	4	KH
2.21	2	0,3
2.23	0,02	0,67
2.24	0,5	>1
2.25	0,3	0,2
2.26	0,2	0,2
2.27	0,02	0,02
2.28	1	2
2.29	2	3
2.30	0,005	0,02
2.31	0,1	0,27
2.32	0,02	0,02
2.33	1	2
2.34	2	0,1
2.35	0,098	0,02
2.36	0,05	0,2
2.37	0,2	
2.38	7	0,2
2.39	0,05	0,03
2.40	0,5	
2.41	1	0,3
2.42	0,5	0,1
2.43	0,02	0,05
2.44	0,3	0,2
2.45	0,1	1
2.46	0,04	0,05
2.47	0,02	1
2.48	0,1	0,5

[Key:]
Beispiel-Nr. = Example No.

Beispiel-Nr.	VEGFR I (FLT)	VEGFR II (KDR)
2.49	0,08	0,05
2.50	KH	KH
2.51		
2.52	0,05	
2.53	0,02	0,02
2.54	0,02	0,005
2.55	0,3	0,2
2.56	0,04	0,02
2.57	KH	KH
2.58	0,5	5
2.59	50	KH
2.60	0,5	0,7
2.61	10	10
2.63		0,0003
2.64	0,04	0,04
2.65		0,0002
2.74	1	KH
2.75	0,3	5
3.0	KH	3,0
3.2	2,0	2,0
4.0	0,5	0,2
8.0	0,04	0,04
8.2	0,2	0,2
8.3	0,05	0,04
8.8	0,05	0,02
8.9	0,5	0,5
8.10	0,02	0,02
8.11	0,2	1

[Key:]
Beispiel-Nr. = Example No.

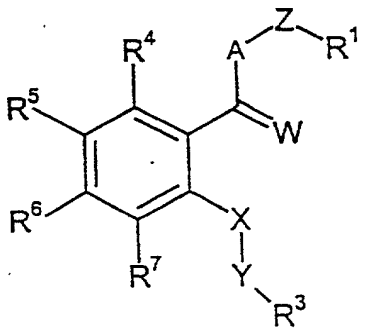
Beispiel-Nr.	VEGFR I (FLT)	VEGFR II (KDR)
8.12	0,2	0,1
8.13	0,5	0,5
8.14	0,5	0,2
8.15	0,2	0,2
8.16	0,2	0,3
8.17		0,05
8.18		0,05

KH= keine Hemmung

[Key:]
Beispiel-Nr. = Example No.
KH = keine Hemmung = No inhibition

Claims

1. Compounds of general formula I



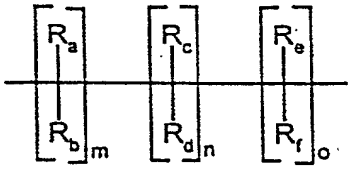
I

in which

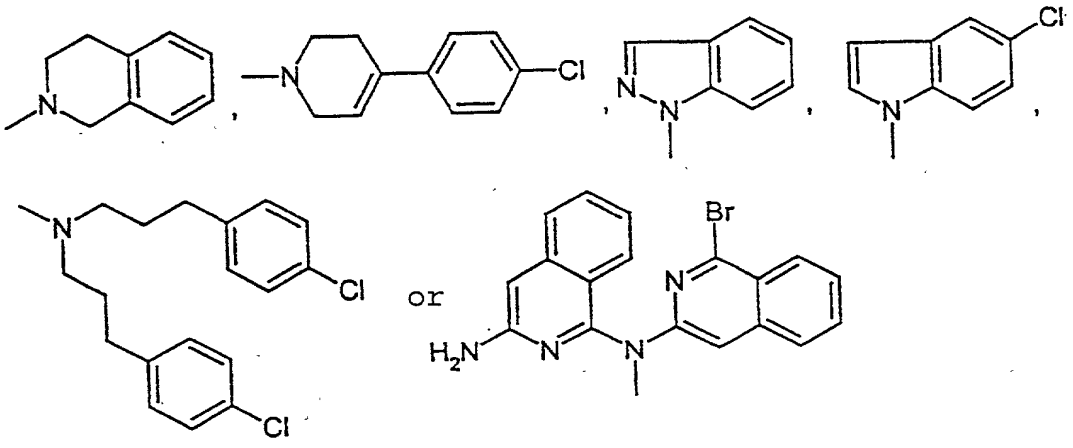
A stands for the group $=NR^2$,

W stands for oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,

Z stands for the group $=NR^{10}$ or =N-, $-N(R^{10})-(CH_2)_q-$, branched or unbranched C_{1-6} alkyl or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

q stands for 1-6,

R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen, C_{1-4} alkyl or the group $=NR^{10}$, and/or R_a and/or R_b can form a bond with R_c and/or R_d or R_c can form a bond with R_e and/or R_f or up to two of radicals R_a-R_f can close a bridge with up to 3 C-atoms each to form R^1 or R^2,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-(CH_2)_p$,

p stands for 1-4,

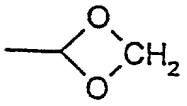
R^1 stands for C_{1-6} alkyl that is unsubstituted or is optionally substituted in one or more places with halogen, C_{1-6} alkyl, in one or more places with halogen, or aryl or

heteroaryl that is substituted with C_{1-6} alkoxy, with the exception of compounds in which aryl is bonded right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or C_{1-6} alkyl or forms a bridge with up to 3 ring members with R_a-R_f from Z or to form R_1,

R^3 stands for monocyclic or bicyclic aryl or heteroaryl that is unsubstituted or optionally substituted in one or more places with halogen, C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy,

R^4, R^5, R^6, and R^7, independently of one another, stand for hydrogen, halogen, or C_{1-6} alkoxy, C_{1-6} alkyl or C_{1-6} carboxylalkyl that is unsubstituted or optionally substituted in one or more places with halogen, or R^5 and R^6 together form the group



R^8, R^9, and R^{10}, independently of one another, stand for hydrogen or C_{1-6} alkyl,

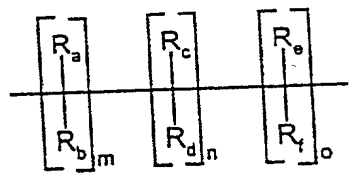
as well as their isomers and salts.

2. Compounds of general formula I, according to claim 1, in which

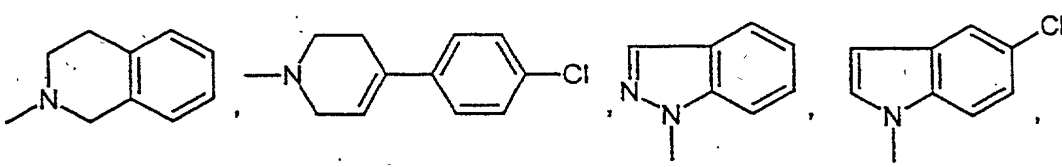
A stands for the group $=NR^2$,

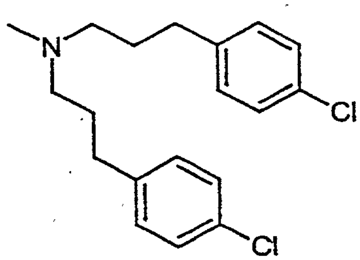
W stands for oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,

Z stands for the group $=NR^{10}$, =N- or $-N(R^{10})-(CH_2)_q-$, branched or unbranched C_{1-6} alkyl or the group

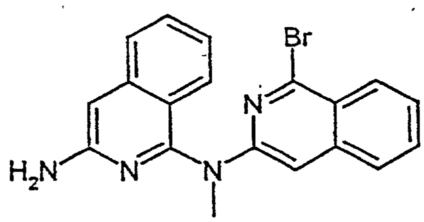


or A, Z and R^1 together form the group





or



m, n, and o stand for 0-3,

q stands for 1-6,

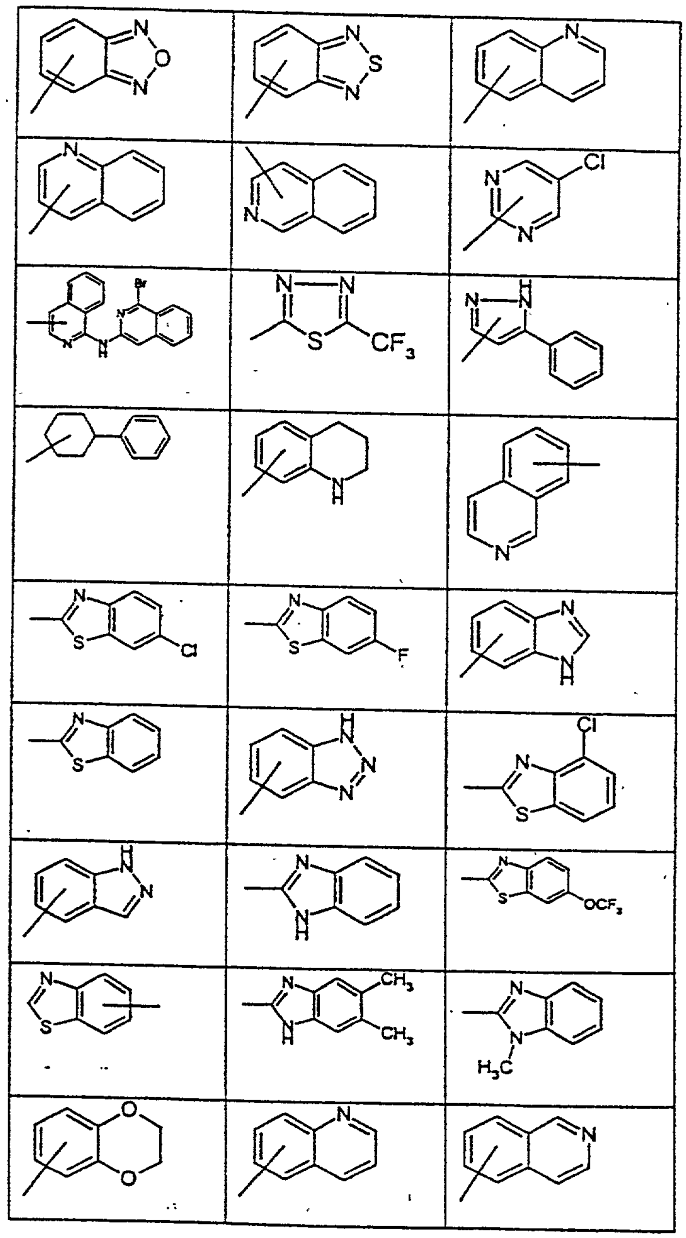
R_a, R_b, R_c, R_d, R_e and R_f, independently of one another, stand for hydrogen, C_{1-4} alkyl or the group $=NR^{10}$,

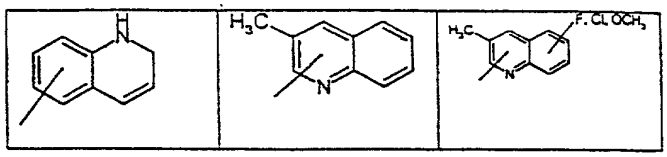
X stands for the group $=NR^9$ or =N-,

Y stands for the group $-(CH_2)_p$,

p stands for 1-4,

R^1 stands for phenyl, pyridiyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group





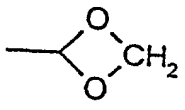
whereby phenyl, substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A

R^2 stands for hydrogen or C_{1-6} alkyl or forms a bridge with up to 3 ring members with R_a-R_f from Z or to form R_1,

R^3 stands for monocyclic or bicyclic aryl or monocyclic or bicyclic heteroaryl that is unsubstituted or optionally substituted in one or more places with halogen, C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy,

R^4, R^5, R^6 and R^7, independently of one another, stand for hydrogen, halogen or C_{1-6} alkoxy or C_{1-6} alkyl that is unsubstituted or optionally substituted in one or more places with halogen,

or R^5 and R^6 together form the group



R^8, R^9 and R^{10}, independently of one another, stand for hydrogen or C_{1-6} alkyl,

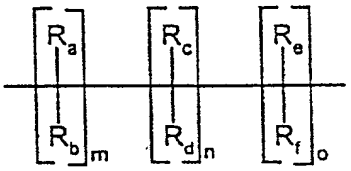
as well as their isomers and salts.

3. Compounds of general formula I according to claims 1 and 2, in which

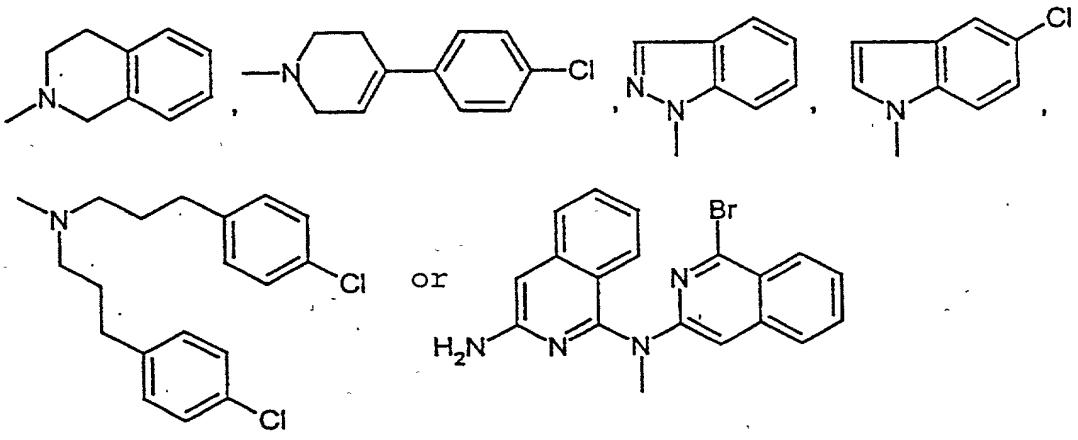
A stands for the group $=NR^2$,

W stands for oxygen, sulfur or two hydrogen atoms,

Z stands for the group $=NR^{10}$, $=N$, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

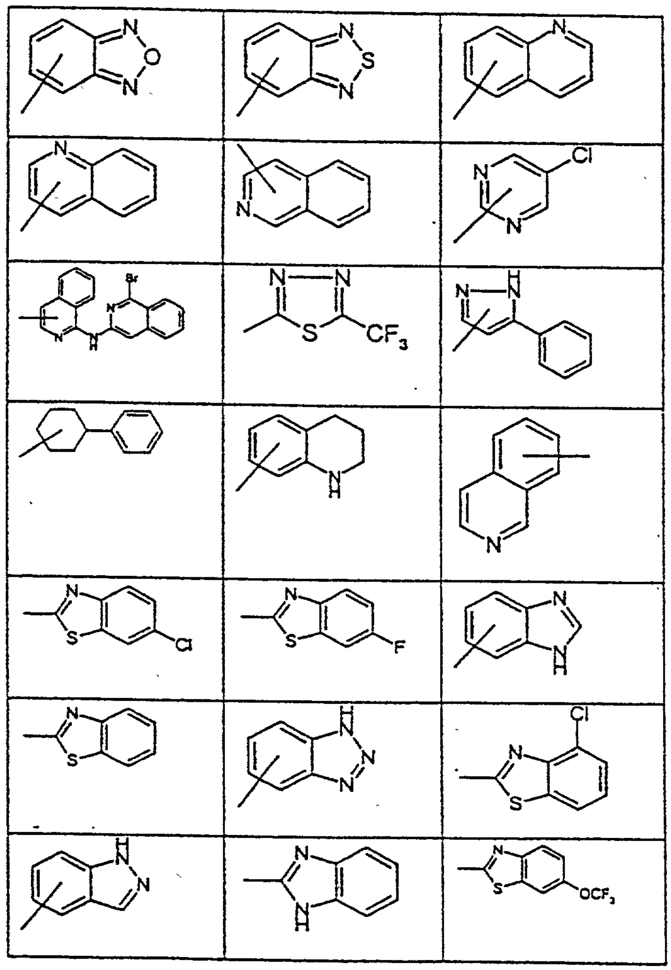
q stands for 1-6,

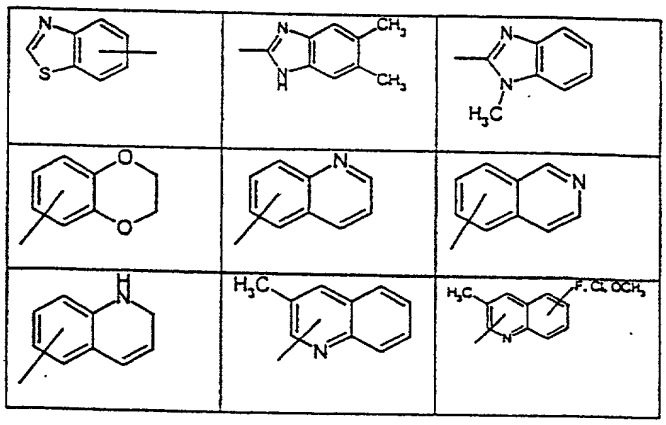
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, p-chlorophenyl, p-methylphenyl, p-methoxyphenyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl, or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, trifluoromethyl, or for the group

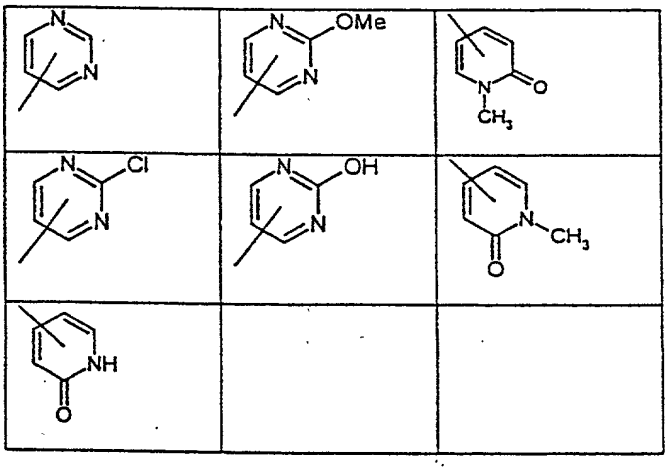




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl, or phenyl, or 1,2,3,4-tetrahydronaphthyl that is substituted by hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

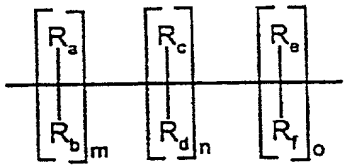
as well as their isomers and salts.

4. Compounds of general formula I according to claims 1 to 3, in which

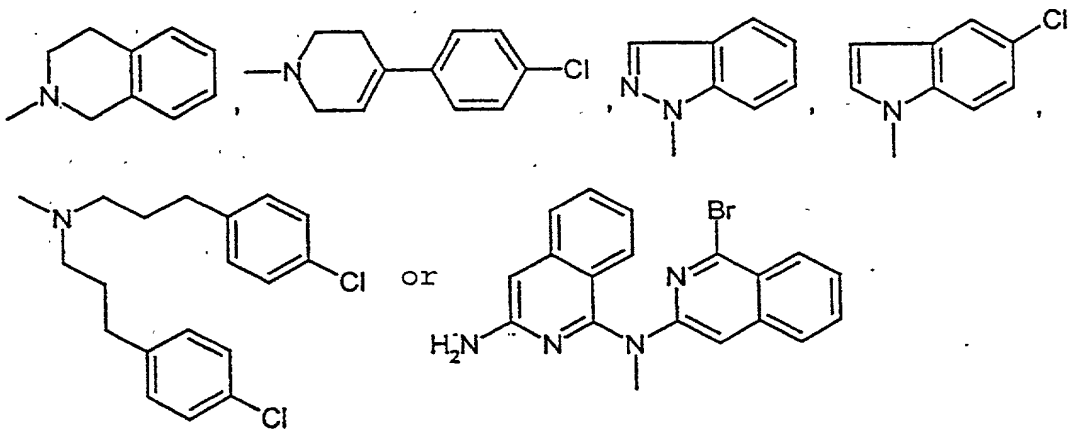
A stands for the group $=NR^2$,

W stands for oxygen,

Z stands for the group $=NR^{10}$, $=N-$, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o stand for 0-3,

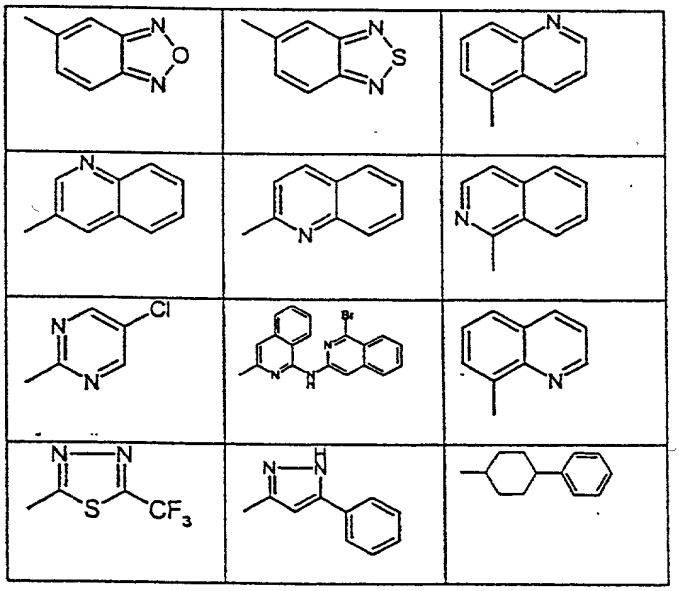
q stands for 1-6,

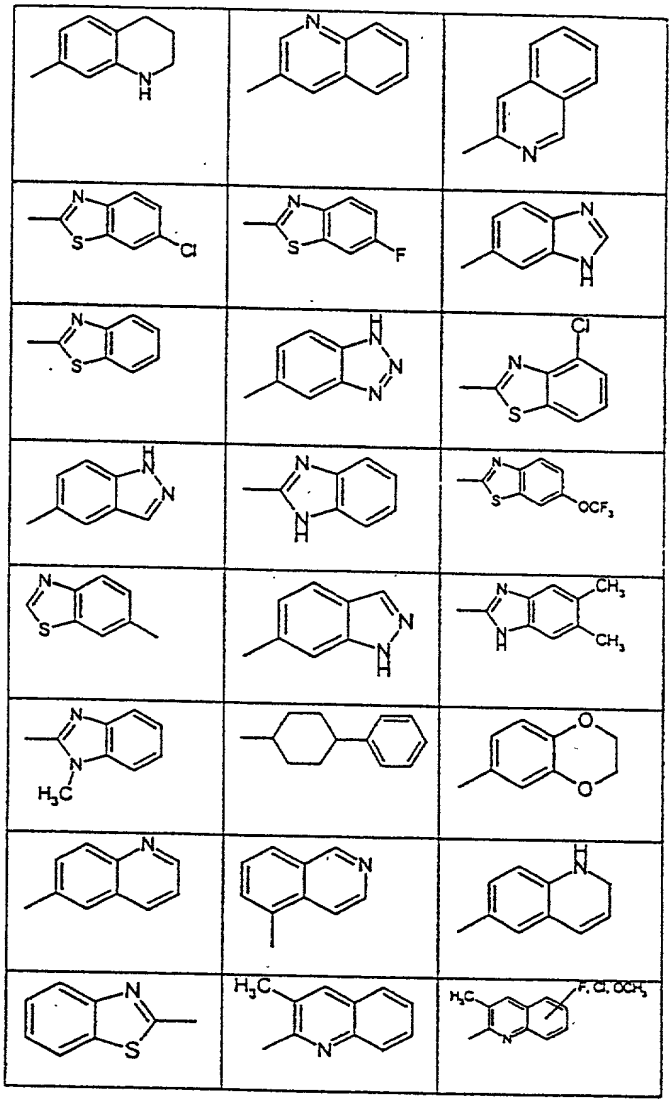
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

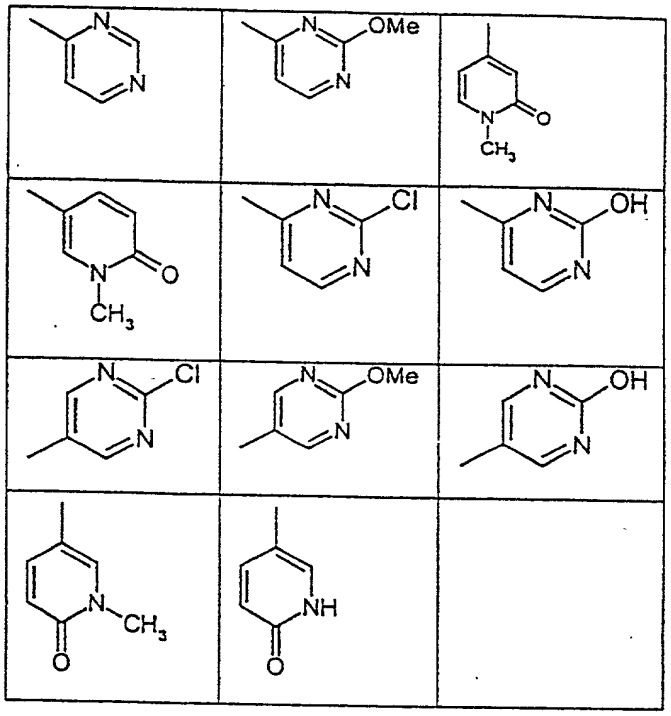




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy, or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

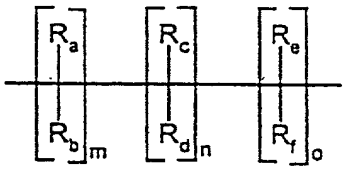
as well as their isomers and salts.

5. Compounds of general formula I according to claims 1 to 3, in which

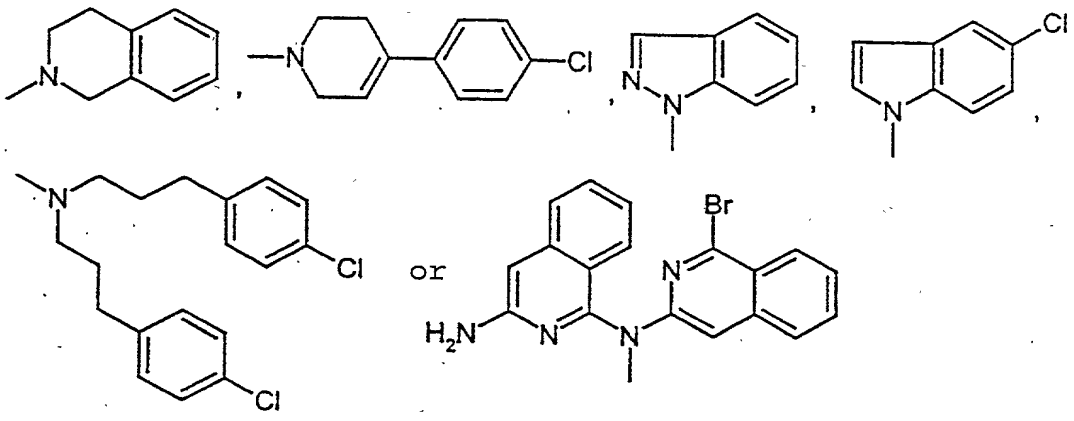
A stands for the group $=NR^2$,

W stands for sulfur,

Z stands for the group $=NR^{10}$, =N-, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z and R^1 together form the group



m, n and o — stand for 0-3,

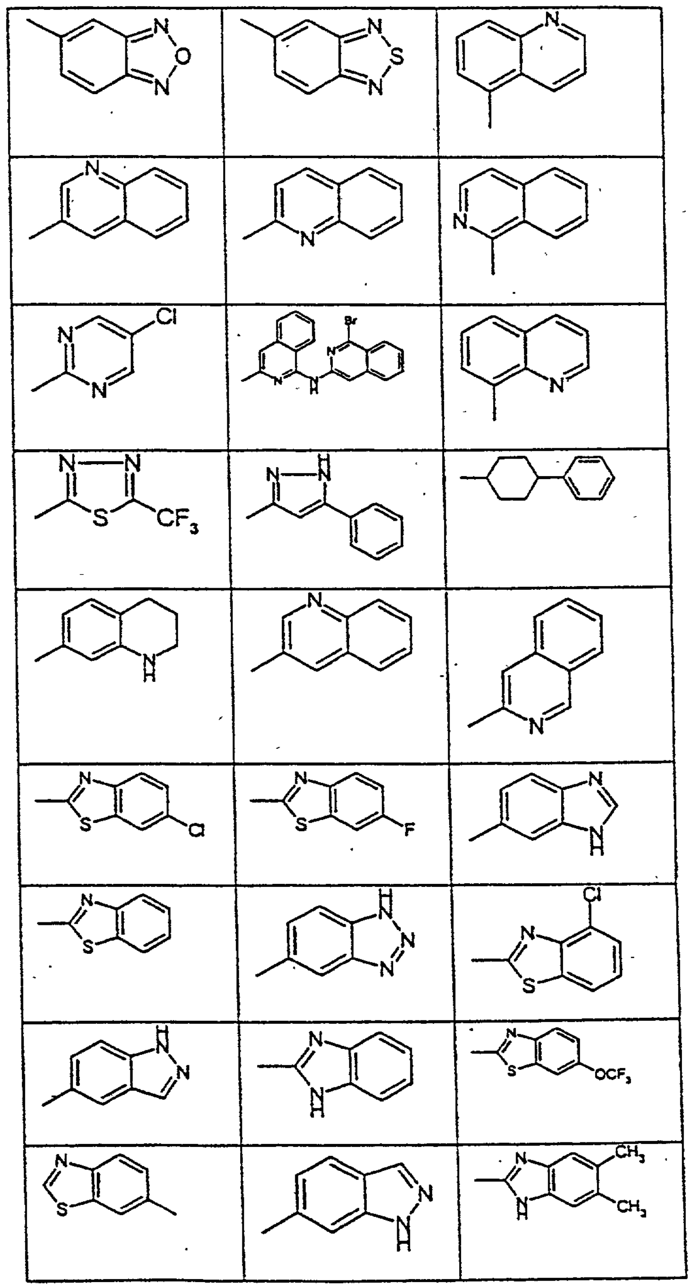
q — stands for 1-6,

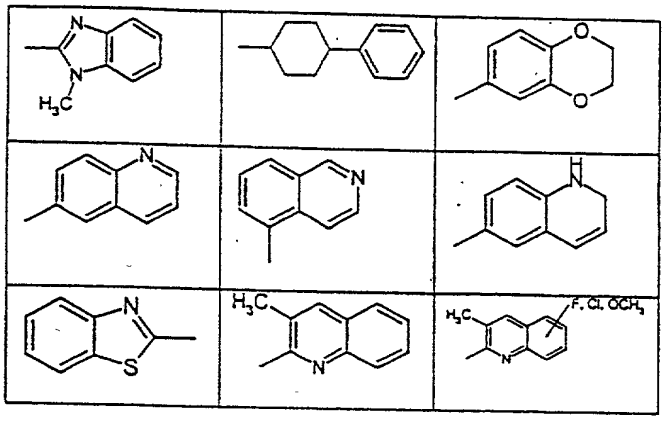
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X — stands for the group $=NR^9$ or =N-,

Y — stands for the group $-CH_2-$,

R^1 — stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

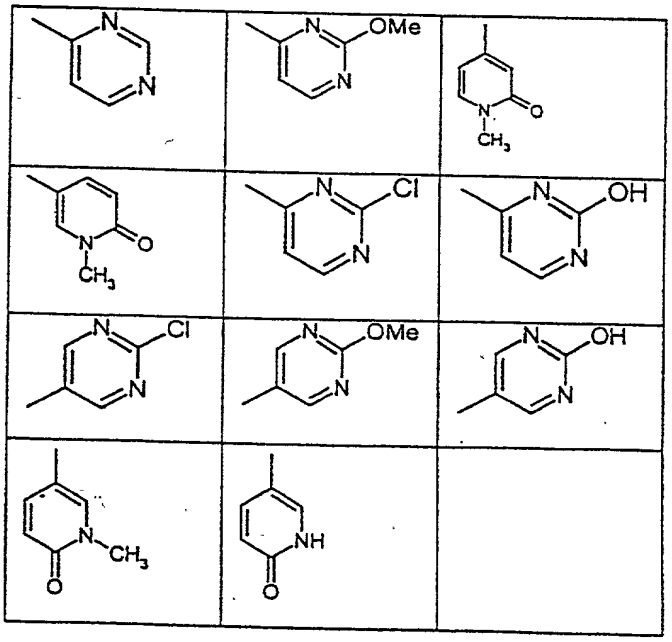




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

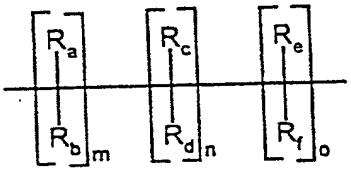
as well as their isomers and salts.

6. Compounds of general formula I according to claims 1 to 3, in which

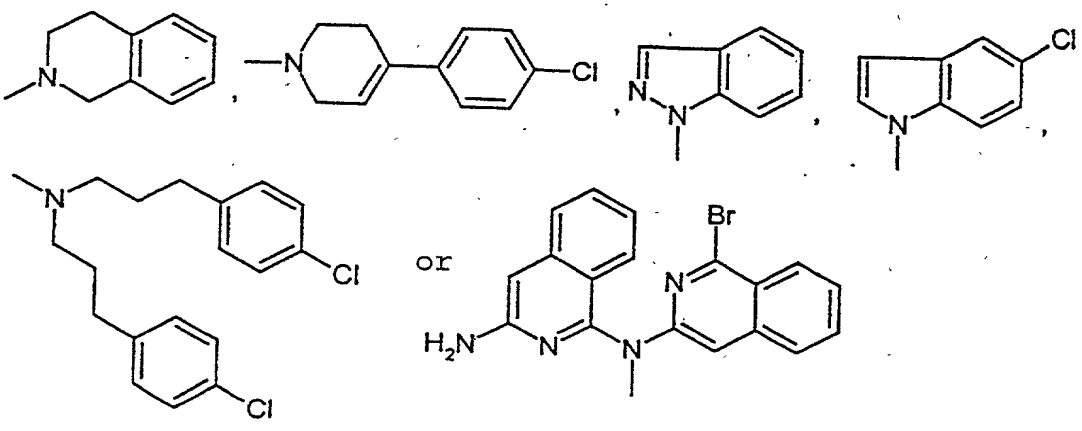
A stands for the group $=NR^2$,

W stands for two hydrogen atoms,

Z stands for the group $=NR^{10}$, $=N-$, $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z, and R^1 together form the group



m, n and o stand for 0-3,

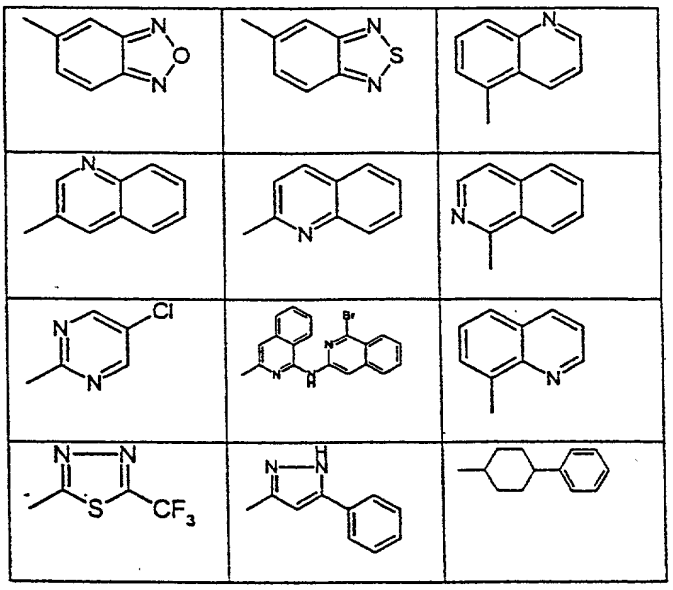
q stands for 1-6,

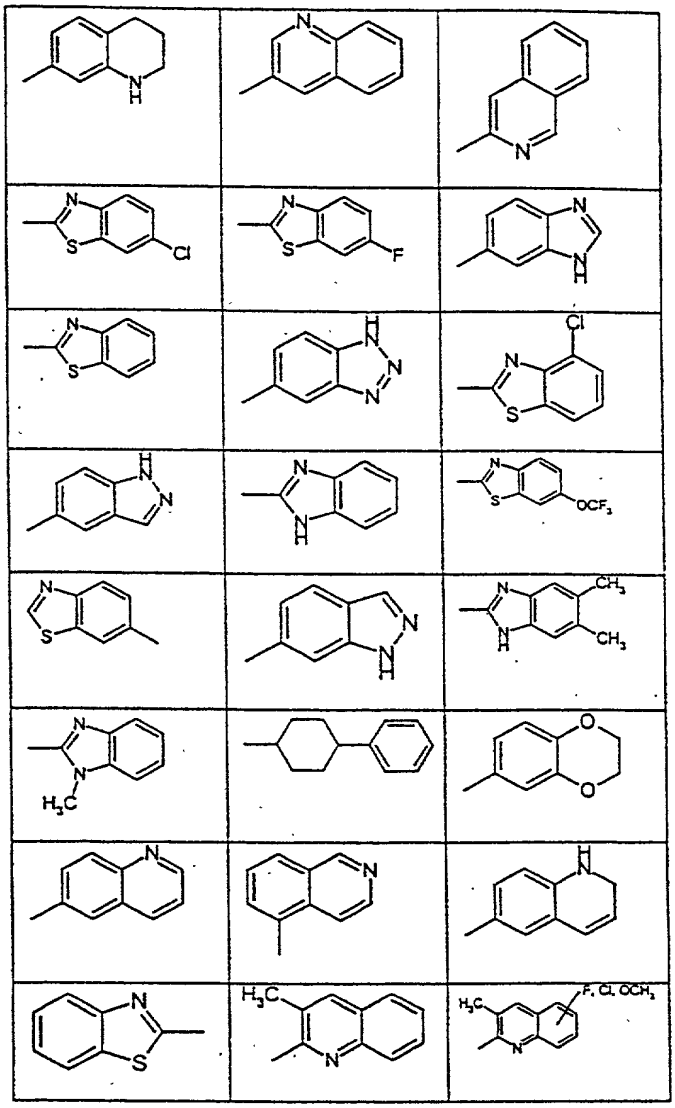
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$ or =N-,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

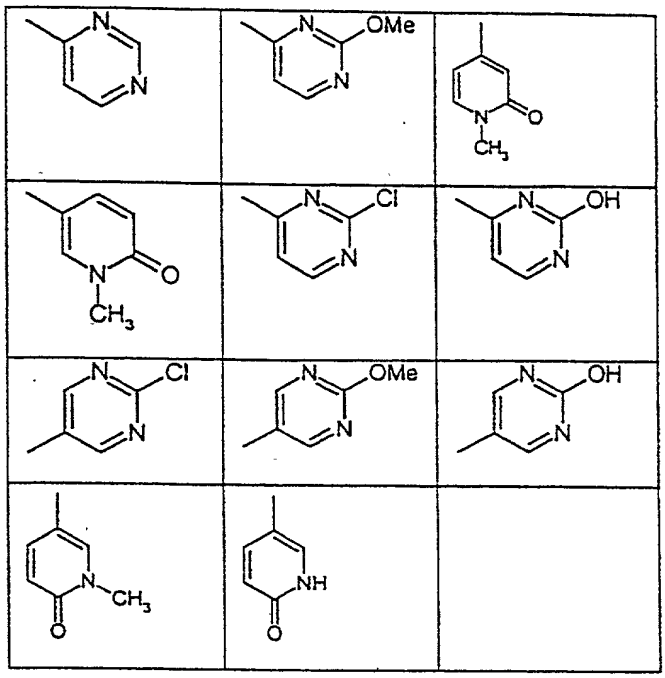




whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^4 and R^7, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^5 and R^6, independently of one another, stand for hydrogen and halogen,

R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

as well as their isomers and salts.

7. Use of the compounds of general formula I, according to claims 1 to 6, for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

8. Pharmaceutical agent that contains at least one compound according to claims 1 to 6.

9. Pharmaceutical agent according to claim 8 for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as

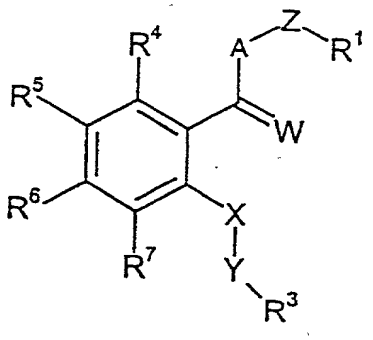
cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

10. Compounds according to claims 1 to 6 and pharmaceutical agents according to claims 6 and 8 with suitable formulations and vehicles.

11. Use of the compounds of formula I according to claims 1 to 6 as inhibitors of tyrosine kinases KDR and FLT.

12. Use of the compounds of general formula I according to claims 1 to 6 in the form of a pharmaceutical preparation for enteral, parenteral and oral administration.

13. Isatoic acid derivatives of general formula V



V,

in which R^3-R^7, X, Y and W have the meanings that are described in general formula I and in which A stands for the group $=NR^2$ or

oxygen, and Z and R^1 together form a =C=O group that is bonded to X, as well as their isomers and salts, as intermediate products for the production of the compounds of general formula I according to the invention.

14. Compounds of general formula V, in which

A and W	stand for oxygen,
Z and R^1	together form a =C=O group that is bonded to X,
X	stands for the group $=NR^9$ or =N-,
Y	stands for the group $-CH_2-$,
R^3	stands for pyridyl, or phenyl or 1,2,3,4-tetrahydronaphthyl that is substituted by hydroxy, bromine, methyl or methoxy,
R^5 and R^6	stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,
R^4 and R^7	stand for hydrogen,
R^9	stands for hydrogen,

as well as their isomers and salts, as intermediate products for the production of compounds of general formula I.

15. Compounds of general formula V according to claims 13 and 14 for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant

rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

Attorney Docket Number: SCH 1806

DECLARATION FOR PATENT APPLICATION

elow named inventor, I hereby declare that:

esidence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ANTRHRANILIC ACID AMIDES AND THE USE THEREOF AS MEDICAMENTS

the specification of which

- ☐ is attached hereto
- ■ was filed on 9 NOVEMBER 1999 as United States Application Number or PCT International Application Number PCT/EP99/08478 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
9824579.8	GREAT BRITAIN	10 NOVEMBER 1998	YES
199 10 396.8	GERMANY	3 MARCH 1999	YES

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

(14) I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James T. Moore (35,619); James E. Ruland (37,432); Jennifer J. Branigan (40,921) and Robert E. McCarthy (46,044)

Declaration for Patent Application (Continued)

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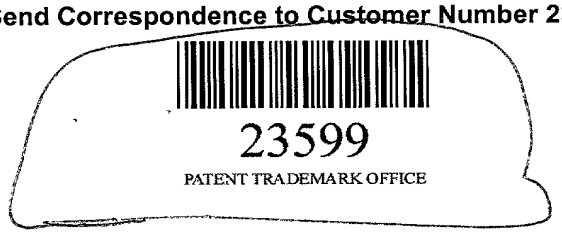

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

100

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Declaration for Patent Application (Continued)

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